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<p>(21) International Application Number: PCT/US99/12093</p> <p>(22) International Filing Date: 1 June 1999 (01.06.99)</p> <p>(30) Priority Data: 60/087,820 3 June 1998 (03.06.98) US 9815175.6 13 July 1998 (13.07.98) GB</p> <p>(71) Applicants (<i>for all designated States except US</i>): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TULARIK, INC. [US/US]; 2 Corporate Drive, S. San Francisco, CA 94080 (US).</p> <p>(72) Inventors; and</p> <p>(75) Inventors/Applicants (<i>for US only</i>): YOUNG, Steven, D. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). EGBERTSON, Melissa [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). PAYNE, Linda, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). WAI, John, S. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). FISHER, Thorsten, E. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GUARE, James, P., Jr. [US/US]; 126 East Lincoln</p>		<p>Avenue, Rahway, NJ 07065 (US). EMBREY, Mark, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). TRAN, Lee [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). ZHUANG, Linghang [CN/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). VACCA, Joseph, P. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). LANGFORD, Marie [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). MELAMED, Jeffrey [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CLARK, David, L. [US/US]; 2 Corporate Drive, S. San Francisco, CA 94080 (US). MEDINA, Julio, C. [US/US]; 2 Corporate Drive, S. San Francisco, CA 94080 (US). JAEN, Juan [US/US]; 2 Corporate Drive, S. San Francisco, CA 94080 (US).</p> <p>(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).</p> <p>(81) Designated States: AE, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: HIV INTEGRASE INHIBITORS</p> <p>(57) Abstract</p> <p>Certain six-membered aromatic and heteroaromatic-dioxo-butyric acid derivatives are described as inhibitors of HIV integrase and inhibitors of HIV replication. These compounds are useful in the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.</p>		

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TITLE OF THE INVENTION
HIV INTEGRASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

5 The present application claims priority to U.S. provisional application Serial No. 60/087,820, filed June 3, 1998.

BACKGROUND OF THE INVENTION

10 A retrovirus designated human immunodeficiency virus (HIV) is the etiological agent of the complex disease that includes progressive destruction of the immune system (acquired immune deficiency syndrome; AIDS) and degeneration of the central and peripheral nervous system. This virus was previously known as LAV, HTLV-III, or ARV. A common feature of retrovirus
15 replication is the insertion by virally-encoded integrase of proviral DNA into the host cell genome, a required step in HIV replication in human T-lymphoid and monocytoid cells. Integration is believed to be mediated by integrase in three steps: assembly of a stable nucleoprotein complex with viral DNA sequences; cleavage of two
20 nucleotides from the 3' termini of the linear proviral DNA; covalent joining of the recessed 3' OH termini of the proviral DNA at a staggered cut made at the host target site. The fourth step in the process, repair synthesis of the resultant gap, may be accomplished by cellular enzymes.

25 Nucleotide sequencing of HIV shows the presence of a pol gene in one open reading frame [Ratner, L. et al., Nature, 313, 277(1985)]. Amino acid sequence homology provides evidence that the pol sequence encodes reverse transcriptase, integrase and an HIV protease [Toh, H. et al., EMBO J. 4, 1267 (1985); Power, M.D. et al.,
30 Science, 231, 1567 (1986); Pearl, L.H. et al., Nature, 329, 351 (1987)]. All three enzymes have been shown to be essential for the replication of HIV.

 It is known that some antiviral compounds which act as inhibitors of HIV replication are effective agents in the treatment of
35 AIDS and similar diseases, e.g., azidothymidine or AZT. Applicants

demonstrate that the compounds of this invention are inhibitors of HIV integrase and inhibitors of HIV replication. The applicants additionally demonstrate that inhibition of integrase in vitro and HIV replication in cells is a direct result of inhibiting the strand transfer
5 reaction catalyzed by the recombinant integrase in vitro and integrase as a component of the preintegration complex in HIV infected cells. The particular advantage of the present invention is highly specific inhibition of HIV integrase and HIV replication. The compounds of the present invention inhibit integrases of closely
10 related lentiviruses such as HIV 2 and SIV, but not integrases from more distantly related retroviruses, for example RSV. These compounds do not inhibit binding or catalysis of other nucleic acid binding proteins, including enzymatic reactions such as those catalyzed by HIV reverse transcriptase, HIV Rnase H, Influenza
15 transcriptase, Hepatitis C polymerase, Yeast DNA polymerase, DNase I, Eco RI endonuclease, or mammalian polymerase II.

Zhao et al., (J. Med. Chem. vol. 40, pp. 937-941 and 1186-1194 (1997)) describe hydrazide and arylamide HIV integrase inhibitors. Bis-catechols useful for inhibiting HIV integrase are
20 described in LaFemina et al. (Antimicrobial Agents & Chemotherapy, vol. 39, no. 2, pp. 320-324, February 1995).

U.S. Patents 4,377,258; 4,336,397; and 4,423,063 as well as Williams and Rooney (J. Med. Chem. vol 26, pp. 1196-1200, 1983) disclose 2,4-dioxo-4-substituted-1-butanoic acid derivatives useful
25 intreating urinary tract calcium oxalate lithiasis. 4-substituted 2,4-dioxobutanoic acid compounds useful for inhibiting an influenza virus endonuclease are described in Tomassini et al. (Antimicrobial Agents & Chemotherapy, vol. 38, no. 12, pp. 2827-2837, December, 1994). 4-phenyl-4-oxo-butenic acid derivatives are disclosed as useful
30 as kynurenine-3-hydroxylase inhibitors for the prevention and/or treatment of neurodegenerative diseases in PCT/EP96/04517, which published as WO 97/17316 and in PCT/EP96/04518, which published as WO 97/17317.

Applicants have discovered that certain six-membered
35 aromatic and heteroaromatic diketo acid derivatives are potent

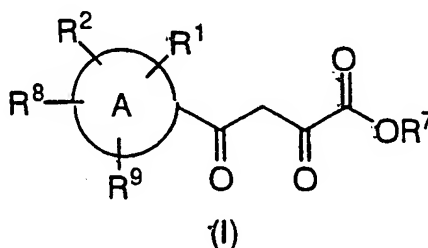
inhibitors of HIV integrase. These compounds are useful in the treatment of AIDS or HIV infection.

SUMMARY OF THE INVENTION

- 5 Compounds of formula I, as herein defined, are disclosed. These compounds are useful in the inhibition of HIV integrase, the prevention of infection by HIV, the treatment of infection by HIV and in the treatment of AIDS and/or ARC, either as compounds, pharmaceutically acceptable salts or hydrates (when appropriate),
 10 pharmaceutical composition ingredients, whether or not in combination with other antivirals, anti-infectives, immunomodulators, antibiotics or vaccines. Methods of treating AIDS, methods of preventing infection by HIV, and methods of treating infection by HIV are also disclosed.

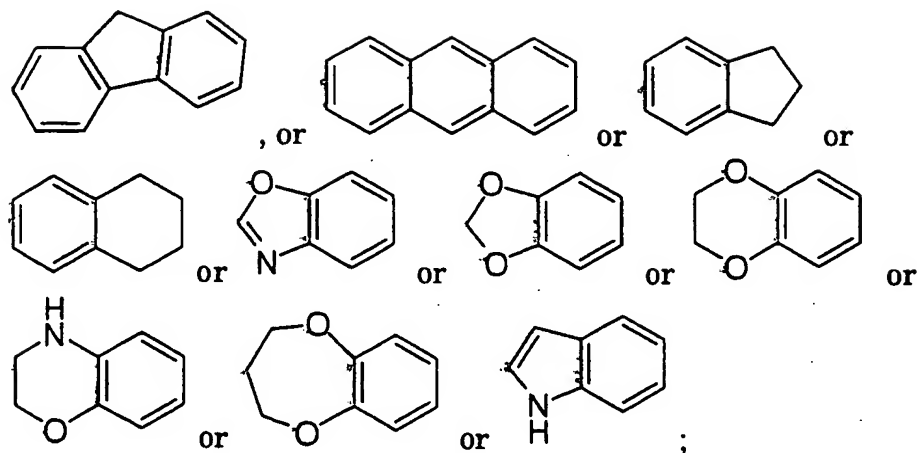
15 DETAILED DESCRIPTION OF THE INVENTION

- This invention is concerned with compounds of formula I, combinations thereof, or pharmaceutically acceptable salts thereof, in the inhibition of HIV integrase, the prevention or treatment of infection by HIV and in the treatment of the resulting acquired immune
 20 deficiency syndrome (AIDS). Compounds of formula I are defined as follows:



and tautomers and pharmaceutically acceptable salts thereof, wherein:

- 25 A is a six-membered aromatic or heteroaromatic ring containing 0, 1, or 2 nitrogen heteroatoms substituted on carbon or nitrogen by R¹, R², R⁸, and R⁹;
 optionally the aromatic ring may be fused with another ring system to form:



R¹ is selected from:

- 5 (1) -H,
- (2) -C₁₋₅ alkyl,
- (3) -C₁₋₆ alkyl-OR⁷,
- (4) -O-C₁₋₆ alkyl-OR⁷,
- (5) -O-C₁₋₆ alkyl-SR⁷,
- 10 (6) -CF₃ or -CH₂CF₃,
- (7) -halo,
- (8) -NO₂,
- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -R⁶,
- 15 (11) -C₂₋₅ alkenyl-R³,
- (12) -C₂₋₅ alkynyl-R³,
- (13) -O-R⁶,
- (14) -O-C₁₋₆ alkyl, wherein one or more of the hydrogen atoms
may be replaced with fluorine atoms,
- 20 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷;
- (16) -O-C₂₋₆ alkyl-N(R⁴)(R⁵);
- (17) -S-C₁₋₃ alkyl;
- (18) -C(O)CH₂C(O)C(O)OR⁷;
- (19) -CH₂-CH(OH)-CH₂-O-R⁷; and
- 25 (20) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

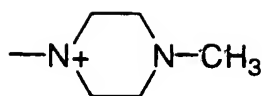
- (1) -H,
- (2) -R³,

- (3) -C₁₋₆ alkyl,
- (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the hydrogen atoms on C₁₋₆ alkyl may be replaced with a fluorine atom,
- 5 (5) -C₂₋₆ alkenyl,
- (6) -O-R⁶,
- (7) -O-C₁₋₆ alkyl-OR⁶,
- (8) -O-C₁₋₆ alkyl-SR⁶,
- (9) -S(O)_n-R⁶,
- 10 (10) -C₁₋₆ alkyl (OR⁶)(R⁴),
- (11) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (12) -C₁₋₆ alkyl S(O)_n-R⁶,
- (13) -C₀₋₆ alkyl C(O)-R⁶,
- (14) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- 15 (15) -C₁₋₆ alkyl C(S)-R⁶,
- (16) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- (17) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (18) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- 20 (1) a 5 or 6 membered aromatic or heteroaromatic ring, containing 0, 1, 2, 3, or 4 heteroatoms selected from oxygen, nitrogen and sulfur, unsubstituted or substituted on nitrogen or carbon by 1 to 5 substituents selected from:
 - (a) halogen,
 - 25 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - 30 (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,

(j)



(k) oxo, and

(l) substituted phenyloxy with 1, 2, or 3 substituents selected from:

- (i) halogen,
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;

10 (2) a 3 to 6 membered saturated ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, unsubstituted or substituted with 1 to 5 substituents selected from:

- 15 (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- (e) -OCF₃,
- (f) -CN,
- 20 (g) =O,
- (h) benzyl, and
- (i) hydroxy;

(3) unsubstituted or substituted hexahydrothieno[3,4-d]imidazolyl with one or two substituents selected from:

- 25 (a) oxo,
- (b) halogen,
- (c) C₁₋₆ alkyl,
- (d) C₁₋₆ alkyloxy-,
- (e) -CF₃,
- 30 (f) -OCF₃,
- (g) -CN, and
- (h) hydroxy;

- 5 (4) a 5 or 6 membered aromatic or heteroaromatic ring,
containing 0, 1, 2 or 3 heteroatoms selected from oxygen,
nitrogen and sulfur, fused with a phenyl ring; wherein the
ring system is unsubstituted or substituted on a nitrogen or
carbon atom by 1 to 3 substituents selected from:
- (a) -halogen,
 - (b) -C₁₋₆ alkyl,
 - (c) -C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - 10 (e) -OCF₃,
 - (f) -CN, and
 - (g) -hydroxy;
- 15 (5) a 3 to 6 membered saturated ring containing 0, 1 or 2
heteroatoms selected from oxygen, nitrogen or sulfur, fused
with a phenyl ring, unsubstituted or substituted with 1 or 2
substituents selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - 20 (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O, and
 - (h) hydroxy;
- 25 (6) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms
selected from oxygen, nitrogen or sulfur, containing 2 or 3
double bonds, unsubstituted or substituted with 1 or 2
substituents selected from:
- (a) halogen,
 - 30 (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - 35 (g) =O, and

- (h) hydroxy; and
- (7) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, containing 2 or 3 double bonds, fused with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:
- (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- (e) -OCF₃,
- (f) -CN,
- (g) =O, and
- (h) hydroxy; and
- each R⁴ is independently selected from:
- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₃ alkyl-R³,
- (7) -C₂₋₃ alkenyl-R³,
- (8) -S(O)_n-R³, and
- (9) -C(O)-R³;
- each R⁵ is independently selected from:
- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₃ alkyl-R³,
- (7) -C₂₋₃ alkenyl-R³,
- (8) -S(O)_n-R³,
- (9) -C(O)-R³,
- (10) -C(O)OR⁴, and
- (11) -C(O)C(O)OH;

each R⁶ is independently selected from:

- (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

each R⁷ is independently selected from:

- 5 (1) -H, and
- (2) -C₁₋₆ alkyl;

R⁸ is selected from:

- (1) -H,
- (2) -O- C₁₋₆ alkyl and
- 10 (3) C₁₋₆ alkyl;

R⁹ is selected from:

- (1) -H,
- (2) -O- C₁₋₃ alkyl,
- (3) -OH, and
- 15 (4) oxo; and

each n is independently selected from 0, 1 and 2.

Also provided for by the present invention are compounds of structural formula (I) wherein: when A is phenyl:

- (1) R¹ is not R⁶ para to the dioxobutyric acid/ester moiety; and
- 20 (2) R² is not selected from:
 - (a) phenyl para to the dioxobutyric acid/ester moiety,
 - (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 - (c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and
 - 25 (d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- (3) at least one of R¹, R², and R⁸ is not:
 - (a) -H,
 - 30 (b) C₁₋₆ alkyl, or
 - (c) R³ wherein R³ is cycloalkyl; and
 - (4) and when R² is S(O)_nR⁶, and R⁶ is CH₂-R³ or R³, then R³ is not unsubstituted phenyl.

Also provided for by the present invention are compounds of formula (I) wherein:

WHEN A is phenyl and R¹ is:

- (a) H,
- (b) C₁₋₅ alkyl,
- (c) halo,
- (d) NO₂,
- (e) R⁶ when R⁶ is CH₂R³ or R³ and when R³ is unsubstituted phenyl,
- (f) -O-C₁₋₆ alkyl, or
- (g) -SC₁₋₃ alkyl;

THEN R² is not selected from:

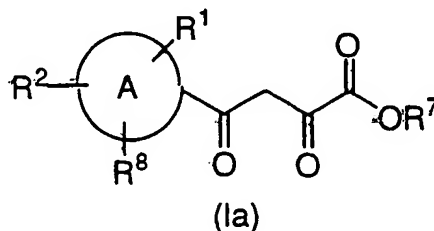
- (a) H,
- (b) R³ when R³ is unsubstituted phenyl,
- (c) C₁₋₆ alkyl,
- (d) CH₂R³ when R³ is unsubstituted phenyl, and
- (e) SOR⁶ when R⁶ is CH₂R³ or R³ and when R³ is unsubstituted phenyl.

Also provided for by the present invention are compounds of formula (I) wherein at least one of R¹, R², R⁸ and R⁹ is not hydrogen.

Also provided for by the present invention are compounds of formula (I) wherein: when A is a fused ring system, the six-membered aromatic ring is substituted by the dioxobutyric acid/ester moiety

Applicants hereby incorporate by reference the disclosure of U.S. provisional application Serial No. 60/087,820, filed June 3, 1998.

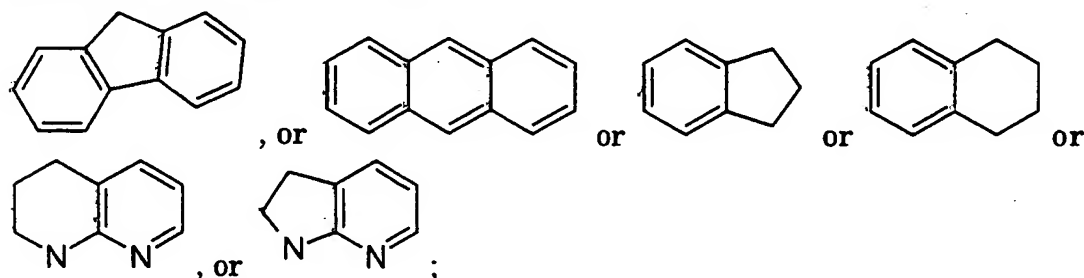
Also provided are compounds of formula Ia, which are defined as follows:



and tautomers and pharmaceutically acceptable salts thereof,

wherein:

A is a six-membered aromatic or heteroaromatic ring containing 0, 1, or 2 heteroatoms selected from nitrogen and substituted on carbon or nitrogen by R¹, R² and R⁸; the aromatic or heteroaromatic ring may optionally be fused with a 5- or 6-membered aromatic or heteroaromatic ring to form a fused ring system, provided that when A is a fused ring system, the six-membered aromatic or heteroaromatic ring is substituted by the dioxobutyric acid/ester moiety; optionally the aromatic or heteroaromatic ring may be fused with another ring system to form:



R¹ is selected from:

- (1) -H,
- (2) -C₁₋₅ alkyl,
- (3) -CF₃,
- (4) -halo,
- (5) -NO₂,
- (6) -N(R⁴)(R⁵),
- (7) -R⁶,
- (8) -C₂₋₅ alkenyl-R³,
- (9) -C₂₋₅ alkynyl-R³,
- (10) -O-R⁶,
- (11) -O-C₁₋₆ alkyl, and
- (12) -C(O)CH₂C(O)C(O)OR⁷;

R² is selected from:

- (1) -H,
- (2) -R³,
- (3) -C₁₋₆ alkyl,
- (4) -C₁₋₆ alkyl substituted with R³,
- (5) -O-R⁶,

- (6) -O-C₁₋₆ alkyl-OR⁶,
 (7) -S(O)_n-R⁶,
 (8) -C₁₋₆ alkyl (OR⁶)(R⁴),
 (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
 5 (10) -C₁₋₆ alkyl S(O)_n-R⁶,
 (11) -C₁₋₆ alkyl C(O)-R⁶,
 (12) -C₁₋₆ alkyl C(S)-R⁶,
 (13) -C₁₋₆ alkyl NR⁴C(O)-R⁶, and
 (14) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵);
 10 each R³ is independently selected from:
- (1) a 5 or 6 membered aromatic or heteroaromatic ring,
 containing 0, 1, 2, 3, or 4 heteroatoms selected from oxygen,
 nitrogen and sulfur, unsubstituted or substituted on a
 nitrogen or carbon atom by 1 to 5 substituents selected from:
- 15 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ alkyloxy-,
 (d) phenyl,
 (e) -CF₃,
 20 (f) -OCF₃,
 (g) -CN,
 (h) hydroxy,
 (i) phenyloxy, and
 (j) substituted phenyloxy with 1, 2, or 3 substituents
 25 selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;
- 30 (2) a 3 to 6 membered saturated ring containing 0 or 1
 heteroatoms selected from oxygen, nitrogen or sulfur,
 unsubstituted or substituted with 1 to 5 substituents selected
 from:
- 35 (a) halogen,
 (b) C₁₋₆ alkyl,

- 5 (c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O,
(h) hydroxy;
- 10 (3) unsubstituted or substituted hexahydrothieno[3,4-
d]imidazolyl with one or two substituents selected from:
(a) oxo,
(b) halogen,
(c) C₁₋₆ alkyl,
(d) C₁₋₆ alkyloxy-,
(e) -CF₃,
(f) -OCF₃,
(g) -CN, and
(h) hydroxy;
- 15 (4) a 5 or 6 membered aromatic or heteroaromatic ring,
containing 0, 1, or 2 heteroatoms selected from oxygen,
nitrogen and sulfur, fused with a phenyl ring; wherein the
20 ring system is unsubstituted or substituted on a nitrogen or
carbon atom by 1 to 3 substituents selected from:
(a) -halogen,
(b) -C₁₋₆ alkyl,
(c) -C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN, and
(g) -hydroxy;
- 25 (5) a 3 to 6 membered saturated ring containing 0 or 1
heteroatoms selected from oxygen, nitrogen or sulfur, fused
with a phenyl ring, unsubstituted or substituted with 1 or 2
30 substituents selected from:
(a) halogen,
(b) C₁₋₆ alkyl,

- (c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
5 (g) =O,
(h) hydroxy;
- (6) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms
selected from oxygen, nitrogen or sulfur, containing 2 or 3
double bonds, unsubstituted or substituted with 1 or 2
10 substituents selected from:
(a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
15 (e) -OCF₃,
(f) -CN,
(g) =O,
(h) hydroxy;
- each R⁴ is independently selected from:
- 20 (1) -H,
(2) -C₁₋₃ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₂₋₃ alkenyl,
25 (6) -C₁₋₃ alkyl-R³,
(7) -C₂₋₃ alkenyl-R³,
(8) -S(O)_n-R³, and
(9) -C(O)-R³;
- each R⁵ is independently selected from:
- 30 (1) -H,
(2) -C₁₋₃ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₂₋₃ alkenyl,
35 (6) -C₁₋₃ alkyl-R³,

(7) -C₂₋₃ alkenyl-R³,

(8) -S(O)_n-R³, and

(9) -C(O)-R³;

each R⁶ is independently selected from:

5 (1) -C₁₋₃ alkyl-R³, and

(2) -R³;

R⁷ is selected from:

(1) -H, and

(2) C₁₋₆ alkyl;

10 R⁸ is selected from:

(1) -H,

(2) -O- C₁₋₆ alkyl, and

(3) C₁₋₆ alkyl; and

each n is independently selected from 0, 1 and 2.

15 Also provided by the present invention are compounds of structural formula (Ia) wherein:

when A is phenyl,

(1) R¹ is not :

- 20 (a) phenyl para to the dioxobutyric acid/ester moiety,
(b) substituted phenyl para to the dioxobutyric acid/ester moiety,
(c) C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety, or
(d) substituted -C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- 25

(2) R² is not selected from:

- (a) phenyl para to the dioxobutyric acid/ester moiety,
(b) substituted phenyl para to the dioxobutyric acid/ester moiety,
30 (c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and
(d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and

(3) at least one of R¹, R², and R⁸ is not:

35 (a) -H,

- (b) C1-6 alkyl, or
 (c) R₃ wherein R₃ is cycloalkyl; and
 (4) and when R¹ or R² is S(O)_nR⁶, R⁶ is R₃.

Particular compounds of structural formula Ia include:

- 5 (1) 3-biphenyl-4-yl-2,4-dioxobutanoic acid,
 (2) 4-(3,5-bis-benzyloxyphenyl)-2-hydroxy-4-oxo-but-2-enoic acid,
 (3) 4-[3-(3,4-difluorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-
 enoic acid,
 (4) 4-[3-(4-methylbenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic
 10 acid,
 (5) 4-(3-benzyloxy-5-methoxyphenyl)-2-hydroxy-4-oxobut-2-enoic
 acid,
 (6) 4-(3-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
 (7) 4-[3-(4-chlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic
 15 acid,
 (8) 4-[3-(3,4-dichlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-
 enoic acid,
 (9) 4-[3-(4-fluorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic
 acid,
 20 (10) 4-[3-(3-chlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic
 acid,
 (11) 4-[3-benzyloxy-5-(6-*tert*-butoxycarbonylamino-
 hexyloxy)phenyl]-2-hydroxy-4-oxobut-2-enoic acid,
 (12) 4-(3-(4-methoxybenzyloxy)phenyl)-4-oxo-2-butenic acid,
 25 (13) 4-(3-benzyloxy-5-hydroxyphenyl)-2-hydroxy-4-oxobut-2-enoic
 acid,
 (14) 4-(3-(1-phenylethoxy)phenyl)-4-oxo-2-butenic acid,
 (15) 4-[3-benzyloxy-5-(6-[5-(2-oxohexahydrothieno[3,4-*d*]imidazol-
 4-yl)pentanoylamino]hexyloxy)-phenyl]-2-hydroxy-4-oxobut-
 30 2-enoic acid,
 (16) 4-[3-(6-aminohexyloxy)-5-benzyloxyphenyl]-2-hydroxy-4-
 oxobut-2-enoic acid,
 (17) 4-(3-dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
 (18) 4-(3-chloro-phenyl)-2,4-dioxobutanoic acid, and
 35 (19) 4-(3-benzyl-phenyl)-2,4-dioxo-butanoic acid,

- (20) 4-(4-dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
(21) 4-(4-benzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
(22) 4-(2-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
(23) 4-naphthalen-1-yl-2,4-dioxobutanoic acid, and
5 (24) 4-naphthalen-2-yl-2,4-dioxobutanoic acid,
(25) 4-(6-benzyloxy-2-oxo-1,2-dihydropyridin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid, and
(26) 4-(2,6-Bis benzyloxypyridin-4-yl)-2,4-dioxobutanoic acid,
(27) 4-[1-(4-fluorobenzyl)-5-indolyl]-2-hydroxy-4-oxo-2-butenic
10 acid,
(28) 4-[1-(4-fluorobenzyl)-4-indolyl]-2-hydroxy-4-oxo-2-butenic acid,
(29) 4-(4-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
(30) 4-[1-(4-fluorobenzyl)-6-indolyl]-2-hydroxy-4-oxo-2-butenic
15 acid, and
(31) 4-biphenyl-4-yl-2,4-dioxobutanoic acid,

and tautomers and pharmaceutically acceptable salts thereof.

Particular compounds of structural formula (I) include:

- (1) 4-(3,5-Bis-benzyloxy-phenyl)-2,4-dioxobutanoic acid,
20 (2) 4-[3-Benzyloxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]-2,4-dioxobutanoic acid,
(3) 4-[3-Benzyloxy-5-(6-*tert*-butoxycarbonylamino-hexyloxy)-phenyl]-2,4-dioxobutanoic acid,
(4) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,
25 (5) 4-[3-(2-chlorobenzyl)phenyl]-2,4-dioxobutanoic acid,
(6) 4-(4-Dibenzylaminophenyl)-2,4-dioxobutanoic acid,
(7) 4-(3-Dibenzylaminophenyl)-2,4-dioxobutanoic acid,
(8) 1-(3-benzyloxy-5-methoxyphenyl)-2,4-dioxobutanoic acid,
(9) 1-(3-Benzyloxyphenyl)-2,4-dioxobutanoic acid,
30 (10) 1-(2-Benzyloxyphenyl)-2,4-dioxobutanoic acid,
(11) 1-[3-(4-Fluorobenzyloxy)phenyl]-2,4-dioxobutanoic acid,
(12) 1-[3-(3,4-Difluorobenzyloxy)phenyl]-2,4-dioxobutanoic acid,
(13) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-
butyric acid,

- (14) 4-{3-[(methyl-phenyl-amino)-methyl]-phenyl}-2,4-dioxo-butyr-
ic acid,
(15) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyr-ic acid,
(16) 2,4-dioxo-4-{3-(1,2,3,4-tetrahydronaphthalen-1-yl)-
phenyl}butyr-ic acid,
5 (17) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyr-ic acid,
(18) 4-{3-(2,4-Difluoro-benzyl)-phenyl}-2,4-dioxo-butyr-ic acid,
(19) 4-{5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl}-2,4-dioxo-
butyr-ic acid,
10 (20) 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyr-ic acid,
(21) 4-{5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl}-2,4-
dioxobutyr-ic acid,
(22) 4-{5-Benzyl-2-(pyridin-2-yloxy)phenyl}-2,4-dioxo-butyr-ic acid,
(23) 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyr-
ic acid,
15 (24) 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyr-ic acid,
(25) 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-
dioxobutyr-ic acid,
(26) 4-{5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl}-2,4-dioxo-
butyr-ic acid,
20 (27) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyr-
ic acid,
(28) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-
dioxobutyr-ic acid,
25 (29) 4-{3-(3-Chloropyridin-2-ylmethyl)phenyl}-2,4-dioxobutyr-
ic acid,
(30) 4-{5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)
phenyl}-2,4-dioxo-butyr-ic acid,
(31) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-
dioxobutyr-ic acid,
30 (32) 4-(3-Benzyl-4-methoxyphenyl)-2,4-dioxobutyr-ic acid,
(33) 4-(5-Benzyl-2-methoxyphenyl)-2,4-dioxobutyr-ic acid,
(34) 4-(3-Benzyl-4-fluorophenyl)-2,4-dioxobutyr-ic acid,
(35) 4-(3-Benzyl-4-N,N-dimethylaminophenyl)-2,4-dioxobutyr-
ic acid,
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- 5
- (36) 4-[5-(2-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid,
- (37) 2,4-Dioxo-4-(3-pyridin-2-ylmethylphenyl)butyric acid,
- (38) 4-(5-Benzyl-3-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid,
- (39) 4-(5-Benzyl-3-methoxyphenyl)-2,4-dioxobutyric acid,
- (40) 4-(5-Benzyl-2-benzyloxy-3-methoxyphenyl)-2,4-dioxobutyric acid,
- 10
- (41) 4-[5-(3-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid,
- (42) 4-[5-Benzyl-3-benzyloxyphenyl]-2,4-dioxobutyric acid,
- (43) 4-[5-Benzyl-2-(2-hydroxy)ethoxyphenyl]-2,4-dioxo-2-butanoic acid,
- (44) 2,4-Dioxo-4-(3-pyridin-3-ylmethylphenyl)butyric acid,
- 15
- (45) 4-[3-(3-Methyl-pyridin-2-ylmethyl)phenyl]-2,4-dioxo-butyric acid,
- (46) 4-(5-Benzyl-2-methylsulfanylphenyl)-2,4-dioxobutyric acid,
- (47) 4-(5-Benzyl-3-N-morpholinophenyl)-2,4-dioxobutyric acid,
- (48) 4-(8-Benzyl-4-methyl-3,4-dihydro-2h-benzo[1,4]oxazin-6-yl)-2,4-dioxobutyric acid,
- 20
- (49) 4-[5-(2-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid,
- (50) 4-[5-(3-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid,
- 25
- (51) 4-(5-Benzyl-2,3,4-trimethoxyphenyl)-2,4-dioxobutyric acid,
- (52) 4-(6-Benzylbenzo[1,3]dioxol-4-yl)-2,4-dioxobutyric acid,
- (53) 4-[3-Benzyl-5-(morpholine-4-carbonyl)phenyl]-2,4-dioxobutyric acid,
- 30
- (54) 4-(3-Benzyl-5-pyridine-2-ylmethylphenyl)-2,4-dioxobutyric acid,
- (55) 4-[3-Benzyl-5-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid,
- (56) 4-(3-Benzyl-5-pyridine-3-ylmethylphenyl)-2,4-dioxobutyric acid,

- (57) 4-[3-Benzyl-5-(2-dimethylamino-1-hydroxy-1-methylethyl)phenyl]-2,4-dioxobutyric acid,
- (58) 4-(5-Benzyl-2-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid,
- 5 (59) 4-(5-Benzyl-2-fluorophenyl)-2,4-dioxobutyric acid,
- (60) 4-(5-Benzyl-3-hydroxymethyl-2-methoxyphenyl)-2,4-dioxobutyric acid,
- (61) 4-[5-Benzyl-2-(pyrazin-2-yloxy)phenyl]-2,4-dioxobutyric acid,
- (62) 4-[3-Benzyl-5-(2-oxopiperidin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid,
- 10 (63) 4-[5-Benzyl-2-methoxy-3-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid,
- (64) 4-[3-(2-Chlorobenzyl)-5-pyridin-2-ylmethylphenyl]-2,4-dioxobutyric acid,
- (65) 4-[5-Benzyl-2-methoxy-3-(4-methylpiperazin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid,
- 15 (66) 4-(5-Benzyl-2-methoxymethylphenyl)-2,4-dioxobutyric acid,
- (67) 4-[3-(2-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- (68) 4-[3-(4-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- 20 (69) 4-[3-(3-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- (70) 4-[5-Benzyl-2-methoxy-3-(tert-butylcarbamoyl)phenyl]-2,4-dioxobutyric acid,
- 25 (71) 4-(3-Benzyl-5-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (72) 4-[5-Benzyl-3-(N'-methyl-N-piperazinyl)phenyl]-2,4-dioxobutyric acid,
- (73) 4-(3-Benzyl-5-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- 30 (74) 4-(6-Benzyl-3-oxo-3,4-dihydro-2-H-benzo[1,4]oxazin-8-yl)-2,4-dioxobutyric acid,
- (75) 4-[5-Benzyl-2-(pyrimidin-2-yloxy)phenyl]-2,4-dioxobutyric acid,
- 35

- (76) 4-(5-Benzyl-3-amino-2-methoxyphenyl)-2,4-dioxobutyric acid,
(77) 4-(5-Benzyl-2-ethoxyphenyl)-2,4-dioxobutyric acid,
(78) 4-[5-Benzyl-2-(2-morpholin-4-yl-ethoxy)phenyl]-2,4-
5 dioxobutyric acid,
(79) 4-(5-Benzyl-2-trifluoroethoxyphenyl)-2,4-dioxobutyric acid,
(80) 4-(5-Benzyl-2-cyclobutyloxyphenyl)-2,4-dioxobutyric acid,
(81) 4-(5-Benzyl-2-cyclopentyloxyphenyl)-2,4-dioxobutyric acid,
(82) 4-(3-Benzyl-5-tetrazol-2-ylmethylphenyl)-2,4-dioxobutyric
10 acid,
(83) 4-(5-Benzyl-2,3-diisopropoxyphenyl)-2,4-dioxobutyric acid,
(84) 4-(5-Benzyl-2-isopropoxy-3-N-methylaminophenyl)-2,4-
dioxobutyric acid,
(85) 4-(5-Benzyl-2-isopropoxy-3-N,N-dimethylaminophenyl)-2,4-
15 dioxo-butyric acid,
(86) 4-[5-Benzyl-2-isopropoxy-3-(2-N,N-
dimethylaminoethoxy)phenyl]-2,4-dioxobutyric acid,
(87) 4-[5-Benzyl-2-isopropoxy-3-(morpholinomethyl)phenyl]-2,4-
dioxo-butyric acid,
(88) 4-(5-Benzyl-2-isopropoxy-3-N,N-
20 dimethylaminomethylphenyl)-2,4-dioxo-butyric acid,
(89) 4-(7-Benzylbenzo[1,3]dioxol-5-yl)-2-hydroxy-4-oxobut-2-enoic
acid,
(90) 2-Hydroxy-4-oxo-4-(3-phenylindan-5-yl)but-2-enoic acid,
(91) 4-(Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
25 (92) 3-(3-Benzyl-5-carboxyacetylphenyl)-3-oxopropionic acid,
(93) 4-(4-Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
(94) 4-(5-Benzyl-3-methoxy-2-methylthioethoxyphenyl)-2,4-
dioxobutyric acid,
(95) 4-(7-Benzyl-2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,4-
30 dioxobutyric acid,
(96) (+/-) 4-(8-Benzyl-3-hydroxy-3,4-dihydro-2H-benzo[B][1,4]di-
oxepin-6-yl)-2,4-dioxobutyric acid,
(97) 4-(2,3-Dimethoxy-5-pent-4-enylphenyl)-2,4-dioxobutyric acid,

- (98) 4-(5-Cyclopropylmethyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
- (99) (6-Benzoyloxy-1-oxo-indan-2-ylidene)-hydroxyacetic acid,
- (100) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (101) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (102) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-dioxobutyric acid,
- (103) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (104) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (105) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-butyric acid,
- (106) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyric acid,
- (107) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (108) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyric acid,
- (109) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (110) 4-[1-(2,6-Difluorobenzyl)-1H-indol-6-yl]-2,4-dioxobutyric acid,
- (111) 4-(1-Benzyl-1H-indol-6-yl)-2,4-dioxobutyric acid,
- (112) 1-[1-(4-Fluorobenzyl)-6-indolyl]-2,4-dioxobutanoic acid,
- (113) 1-[1-(4-Fluorobenzyl)-4-indolyl]-2,4-dioxobutanoic acid,
- (114) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (115) 2,4-Dioxo-4-[3-(2,6-difluoro-benzyl)-phenyl]-butyric acid,
- (116) 2,4-Dioxo-4-[3-(2,4,6-trifluoro-benzyl)-phenyl]-butyric acid,
- (117) 2,4-Dioxo-4-[3-(2-fluoro-3-chloro-benzyl)-phenyl]-butyric acid,
- (118) 2,4-Dioxo-4-[3-(2-methyl-4-fluoro-benzyl)-phenyl]-butyric acid,
- (119) 4-[3-(2,3-Dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (120) 4-[3-(2-Chloro-3-methylbenzyl)phenyl]-2,4-dioxobutyric acid,
- (121) 2,4-Dioxo-4-[3-(2,6-dichloro-benzyl)-phenyl]-butyric acid,

- (122) 2,4-Dioxo-4-[3-(2,3,4,5,6-penta-fluoro-benzyl)-phenyl]-butyric acid,
- (123) 4-[3-(2-Fluorobenzyl)phenyl]-2,4-dioxobutyric acid,
- (124) 2,4-Dioxo-4-[3-(2-chloro-4-fluoro-benzyl)-phenyl]-butyric acid,
- 5 (125) 4-[3-(2-Methylbenzyl)phenyl]-2,4-dioxobutyric acid,
- (126) 2,4-Dioxo-4-[3-(2-methoxybenzyl)phenyl]butyric acid,
- (127) 4-[3-(2-Chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
- (128) 4-[3-(2-Bromobenzyl)phenyl]-2,4-dioxobutyric acid,
- (129) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-
- 10 butyric acid,
- (130) 4-[3-(3-Chloro-2-methyl-benzyl)phenyl]-2,4-dioxobutyric acid,
- (131) 4-[3-(2,3-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (132) 4-(3,5-Dibenzylphenyl)-2,4-dioxo-butyric acid,
- (133) 2,4-Dioxo-4-[3-(2-trifluoromethylbenzyl)phenyl]butyric acid,
- 15 (134) 4-[3-(4-Fluorobenzyl)phenyl]-2,4-dioxobutyric acid,
- (135) 4-[3-(3-Chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
- (136) 2,4-Dioxo-4-[3-(2-bromo-3-chloro-benzyl)-phenyl]-butyric acid,
- (137) 4-(3-Benzylphenyl)-2,4-dioxo-butyric acid,
- 20 (138) 4-[3-(2-Fluoro-3-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (139) 4-[3-(3-Chloro-4-fluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (140) 2,4-Dioxo-4-[3-(2-bromo-4-fluoro-benzyl)-phenyl]-butyric acid,
- 25 acid,
- (141) 4-[3-(3-Bromobenzyl)phenyl]-2,4-dioxobutyric acid,
- (142) 4-[3-(2,5-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (143) 4-[3-(5-Chloro-2-fluoro-benzyl)phenyl]-2,4-dioxobutyric acid,
- (144) 4-[3-(3-Methylbenzyl)phenyl]-2,4-dioxobutyric acid,
- 30 (145) 4-(3-Benzyl-4-methyl-phenyl)-2,4-dioxo-butyric acid,
- (146) 4-[3-(3,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (147) 4-[3-(2,5-Dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (148) 4-[3-(2-Chloro-6-methyl-benzyl)phenyl]-2,4-dioxobutyric acid,
- (149) 2,4-Dioxo-4-[3-(2-trifluoromethyl-4-chloro-benzyl)-phenyl]-
- 35 butyric acid,

- (150) 4-[3-(2-Bromo-5-chloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (151) 4-(3-Naphthalen-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
- (152) 2,4-Dioxo-4-[3-(3-fluorobenzyl)phenyl]butyric acid,
- 5 (153) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
- (154) 2,4-Dioxo-4-[3-(1-phenylethyl)phenyl]butyric acid,
- (155) 4-(3-Benzyl-4,5-dimethylphenyl)-2,4-dioxo-butyric acid,
- (156) 2,4-Dioxo-4-[3-(3-methoxybenzyl)phenyl]butyric acid,
- (157) 4-[3-(5-Methyl-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyric acid,
- 10 (158) 4-[3-(5-Chloro-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyric acid,
- (159) 4-(3-Benzyl-5-methylphenyl)-2,4-dioxo-butyric acid,
- (160) 4-[3-(2-Cyanobenzyl)phenyl]-2,4-dioxo-butyric acid,
- 15 (161) 4-[3-Benzylphenyl]-2,4-dioxobutyric acid,
- (162) 4-[3-(3,5-Dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (163) 4-(5-Benzyl-2,4-dimethylphenyl)-2,4-dioxo-butyric acid,
- (164) 4-(5-Benzyl-2-methylphenyl)-2,4-dioxo-butyric acid,
- (165) 4-(3-Cyclohexylmethyl-phenyl)-2,4-dioxo-butyric acid,
- 20 (166) 4-[3-[(Methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-butyric acid,
- (167) 4-[3-Benzyl-5-(5-hydroxy-pentyl)-phenyl]-2,4-dioxo-butyric acid,
- (168) 4-(3-Benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
- 25 (169) 4-[3-(3-tert-Butoxy-2-hydroxy-propyl)-5-(2-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (170) 2,4-Dioxo-4-[3-(2,3-dimethoxy-benzyl)-phenyl]-butyric acid,
- (171) 4-[3-(Methoxyphenylmethyl)phenyl]-2,4-dioxobutyric acid,
- (172) 4-[3-[Hydroxy-(tetrahydro-furan-3-yl)-methyl]-5-(2-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- 30 (173) 2,4-Dioxo-4-(3-phenoxyethyl-phenyl)-butyric acid,
- (174) 2,4-Dioxo-4-(3-phenoxyethyl-phenyl)-butyric acid
- (175) 4-[3-Benzyl-5-(cyclopropylcarboxamido)-phenyl]-2,4-dioxobutyric acid,

- (176) 4-[3-Benzyl-5-(t-butoxycarbamoyl)phenyl]-2,4-dioxobutyric acid,
- (177) 4-[3-(Hydroxy-phenyl-methyl)-phenyl]-2,4-dioxo-butyric acid,
- (178) 4-(5-Benzyl-2,3-dimethylphenyl)-2,4-dioxo-butyric acid,
- 5 (179) n-[3-(3,5-Dibromobenzyl)phenyl]-2,4-dioxo-butyric acid,
- (180) 4-[3-(2-Methyl-benzyl)-5-pyrimidin-2-yl-phenyl]-2,4-dioxo-butyric acid,
- (181) 4-[3-Benzyl-2-(pyrimidin-2-ylamino)-phenyl]-2,4-dioxo-butyric acid
- 10 (182) 4-[3-Benzoimidazol-1-ylmethyl-5-(2-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (183) 2,4-Dioxo-4-[3-(3-trifluoromethylbenzyl)phenyl] butyric acid,
- (184) 4-(4-Phenoxy-phenyl)-2,4-dioxo-butyric acid,
- (185) 2,4-Dioxo-4-(3-[1,2,3]triazol-2-ylmethyl-phenyl)-butyric acid,
- 15 (186) 4-[3-Benzyl-5-(6-methoxy-pyridin-2-yl)-phenyl]-2,4-dioxo-butyric acid,
- (187) 4-(3-Benzotriazol-2-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
- (188) 4-[3-Benzyl-5-(2-(4-methylpiperazin-1-yl)-pyrazin-6-yl)phenyl]-2,4-dioxobutyric acid,
- 20 (189) 4-[4-(3-Phenethyl)phenyl]-2,4-dioxobutyric acid,
- (190) 4-[4-(3-Chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
- (191) 4-(3-Benzoimidazol-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
- (192) 4-[3-Benzyloxy-5-(6-tert-butoxycarbonylamino-hexyloxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid,
- 25 (193) 4-(3-Benzotriazol-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
- (194) 4-[3-(3,5-Dimethyl-pyrazol-1-ylmethyl)-phenyl]-2,4-dioxo-butyric acid,
- (195) 4-[3-Benzyloxy-5-(2-morpholin-4-yl-ethoxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid,
- 30 (196) 4-(4-Methyl-3-phenoxy-phenyl)-2,4-dioxo-butyric acid
- (197) 4-[3-(2-Hydroxy-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (198) 4-[3-Benzyl-5-(6-dimethylamino-pyrazin-2-yl)-phenyl]-2,4-dioxo-butyric acid, and
- 35 (199) 4-(5-Benzyl-2-methoxypyridin-3-yl)-2,4-dioxobutyric acid;

and tautomers and pharmaceutically acceptable salts thereof.

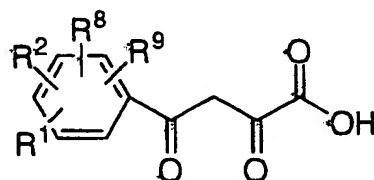
One class of compounds of structural formula (I) includes:

- (1) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,
- (2) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-
5 butyric acid,
- (3) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-
butyric acid,
- (4) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
- (5) 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-
10 phenyl]butyric acid,
- (6) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
- (7) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (8) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-
butyric acid,
- (9) 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyric acid,
- (10) 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-
dioxobutyric acid,
- (11) 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (12) 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric
20 acid,
- (13) 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
- (14) 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-
dioxobutyric acid,
- (15) 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-
25 butyric acid,
- (16) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric
acid,
- (17) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-
dioxobutyric acid,
- (18) 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric
30 acid,
- (19) 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)
phenyl]-2,4-dioxo-butyric acid,
- (20) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-
35 dioxobutyric acid,

- (21) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-
2,4-dioxobutyric acid,
- (22) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-
2,4-dioxobutyric acid,
- 5 (23) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-
methoxyphenyl]-2,4-dioxobutyric acid,
- (24) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (25) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (26) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-
10 dioxo-butyric acid,
- (27) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-
dioxo-butyric acid,
- (28) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-
butyric acid,
- 15 (29) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-
butyric acid, and
- (30) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)
phenyl]-2,4-dioxo-butyric acid;

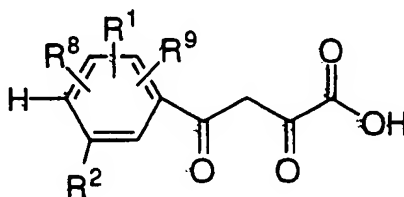
and tautomers and pharmaceutically acceptable salts thereof.

- 20 One class of compounds of the present invention is
represented by the structural formula below:

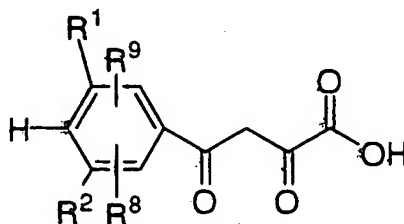


Another class of compounds of the present invention is
represented by the structural formula below:

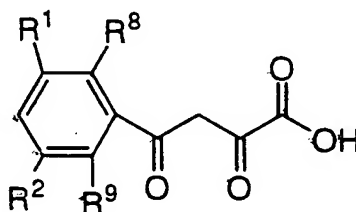
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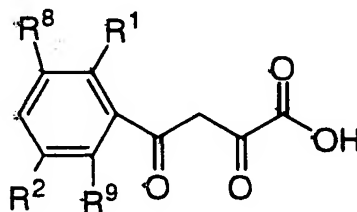
Another class of compounds of the present invention is represented by the following structural formula:



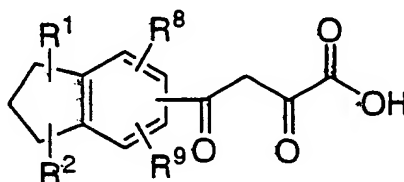
5 Still another class of compounds of the present invention is represented by the formula below:



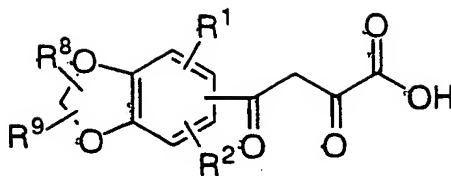
Another class of compounds of the present invention is represented by the following structural formula:



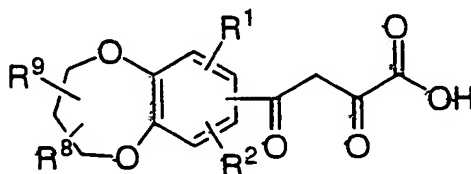
10 Yet another class of compounds of the present invention is represented by the following structural formula:



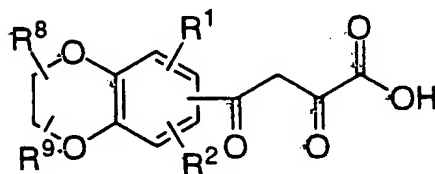
Still another class of compounds of the present invention is represented by the following structural formula:



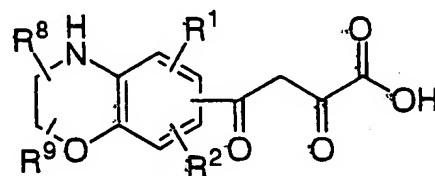
Another class of compounds of the present invention is represented by the following structural formula:



5 Yet another class of compounds of the present invention is represented by the following structural formula:

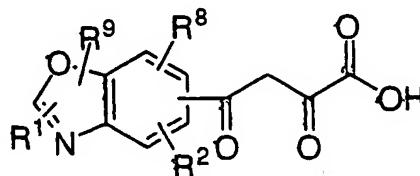


Still another class of compounds of the present invention is represented by the following structural formula:

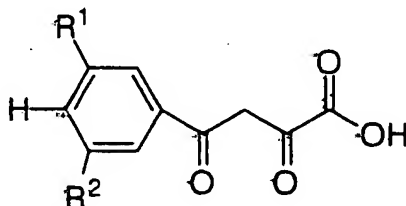


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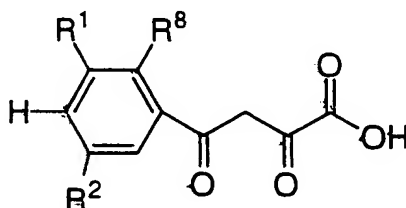
Another class of compounds of the present invention is represented by the following structural formula:



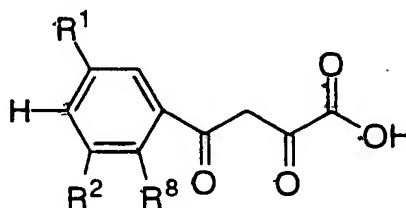
Yet another class of compounds of the present invention is represented by the following structural formula:



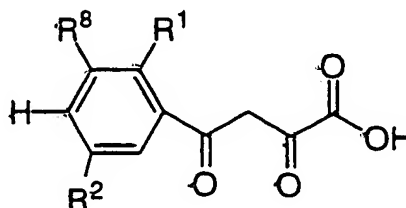
5 Still another class of compounds of the present invention is represented by the following structural formula:



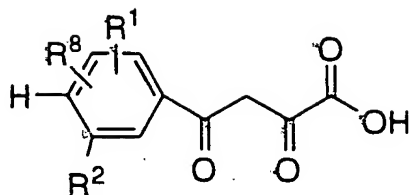
Another class of compounds of the present invention is represented by the following structural formula:



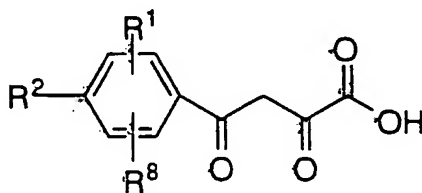
10 Still another class of compounds of the present invention is represented by the following structural formula:



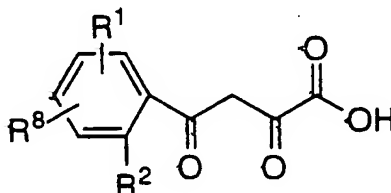
One class of compounds of the present invention is represented by the structural formula below:



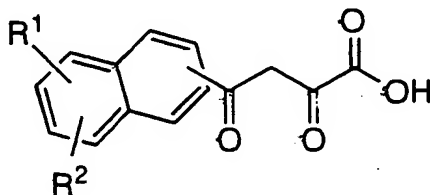
Another class of compounds of the present invention is represented by the following structural formula:



5 Still another class of compounds of the present invention is represented by the formula below:

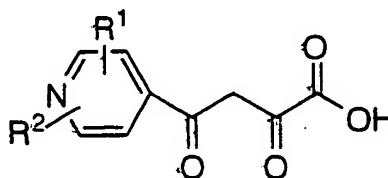


Another class of compounds of the present invention is represented by the following structural formula:

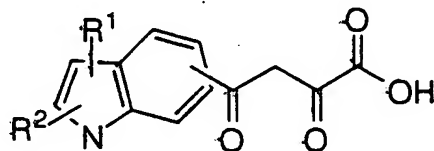


10

Another class of compounds of the present invention is represented by the following structural formula:

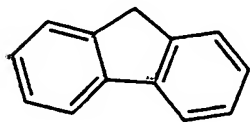


Another class of compounds of the present invention is represented by the following structural formula:

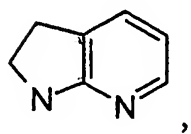


5 In one embodiment of the present invention, A is selected from:

- (1) phenyl,
- (2) pyridyl,
- (3) naphthyl,
- 10 (4) indolyl, provided that the aryl ring is substituted by the dioxobutyric acid/ester moiety in structural formula (I),
- (5)

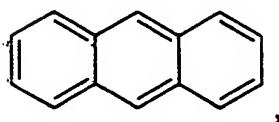


(6)

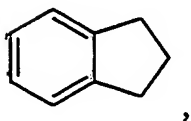


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(7)

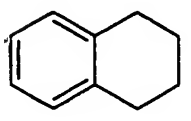


(8)

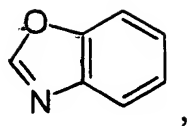


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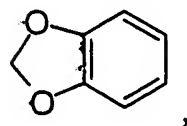
(9)



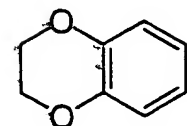
(10)



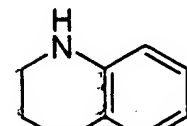
(11)



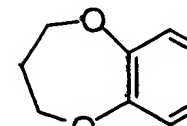
(12)



(13)

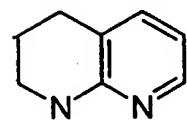


(14)



(15)

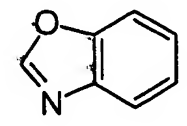
, and



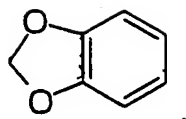
In another embodiment of the present invention, A is selected from:

- (1) phenyl,
- (2) pyridinyl,
- (3) indolyl, provided that 6-membered aromatic ring is substituted by the dioxobutyric moiety in structural formula (I);

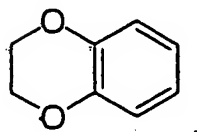
(4)



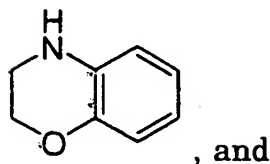
(5)



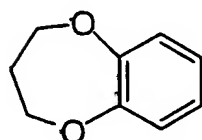
(6)



(7)



(8)



5

In still another embodiment of the present invention, A is phenyl.

10

from:

In one embodiment of the present invention, R¹ is selected

15

- (1) -H,
- (2) -C₁₋₅ alkyl,
- (3) -C₁₋₆ alkyl-OR⁷;
- (4) -O-C₁₋₆ alkyl-OR⁷,
- (5) -O-C₁₋₆ alkyl-SR⁷,
- (6) -CF₃ or -CH₂CF₃,
- (7) -F, Cl, or Br,,
- (8) -NO₂,
- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -phenyl,
- (11) substituted phenyl substituted with 1 or 2 substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,

20

25

- (d) phenyl,
 (e) -CF₃,
 (f) -OCF₃,
 (g) -CN,
 5 (h) hydroxy,
 (i) phenyloxy, and
 (j) substituted phenyloxy with 1, 2, or 3 substituents
 selected from:
 (i) halogen,
 10 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;
- (12) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
 unsubstituted or substituted with 1 to four substituents
 15 independently selected from:
 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 20 (d) phenyl,
 (e) -CF₃,
 (f) -SCH₃,
 (g) -CN,
 (h) hydroxy,
 25 (i) phenyloxy,
 (j) -C₀₋₆ alkyl-N(R⁷)₂,

$$\text{—N} \begin{array}{c} \diagup \quad \diagdown \\ | \quad | \\ \diagdown \quad \diagup \end{array} \text{N—CH}_3$$

 (k) , and
 (l) substituted phenyloxy with 1, 2, or 3 substituents
 selected from:
 30 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;

- (13) -O-R₆,
- (14) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three fluorine atoms,
- (15) -O-C₁₋₆ alkyl-NH-C(O)-OR₇;
- 5 (16) -O-C₂₋₆ alkyl-N(R₄)(R₅);
- (17) -S-C₁₋₃ alkyl;
- (18) -C(O)CH₂C(O)C(O)OR₇;
- (19) -CH₂-CH(OH)-CH₂-O-R₇; and
- (20) -C(OH)(CH₃)-CH₂N(R₄)(R₅).

10 In another embodiment of the present invention, R¹ is selected from:

- (1) -H,
- (2) -CH₃,
- (3) -C₁₋₆ alkyl-OR₇;
- 15 (4) -O-C₁₋₆ alkyl-OR₇,
- (5) -O-C₁₋₆ alkyl-SR₇,
- (6) -CF₃ or -CH₂CF₃,
- (7) -Cl,
- (8) -F,
- 20 (9) -C₀₋₃ alkyl -N(R₄)(R₅),
- (10) -phenyl,
- (11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- 25 (a) -F, -Cl, or -Br,
- (b) CH₃,
- (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
- (d) -CF₃,
- (e) -SCH₃,
- 30 (f) -CN,
- (g) hydroxy,
- (h) -C₀₋₆ alkyl-N(R₇)₂,

- (12) -O-CH₂-phenyl, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- (a) -F, -Cl, or -Br,
 - (b) -CH₃,
 - (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 - (d) -CF₃,
 - (e) -SCH₃,
 - (f) -CN,
 - (g) hydroxy,
 - (h) -C₀₋₆ alkyl-N(R⁷)₂,
- (13) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three fluorine atoms, and
- (14) -C(O)CH₂C(O)C(O)OH;
- (15) (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷;
- (16) -O-CH₂CH₂ N(CH₃)₂,
- (17) -O-CH(CH₃)CH₂N(CH₃)₂,
- (18) -O-CH₂CH₂ NH₂,
- (19) -O-CH(CH₃)CH₂NH₂,
- (20) (20) -S-CH₃,
- (21) -C(O)CH₂C(O)C(O)OH,
- (22) -CH₂-CH(OH)-CH₂-O-R⁷, and
- (23) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵).

In yet another embodiment of the present invention, R¹ is selected from:

- (1) -H,
- (2) -CH₃,
- (3) -CH₂OCH₃,
- (4) -OCH₂CH₂OH,
- (5) -OCH₂CH₂OCH₃,
- (6) -(CH₂)₆-OH,
- (7) -CF₃,
- (8) -F,
- (9) -Cl,

- (10) -C₀₋₃ alkyl -N(R⁴)(R⁵),
 (11) -phenyl,
 (12) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
 5 unsubstituted or substituted with 1 to four substituents
 independently selected from:
 (a) -F, -Cl, or -Br,
 (b) CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 (d) -CF₃,
 10 (e) -CN,
 (f) hydroxy,
 (g) -C₀₋₆ alkyl-N(R⁷)₂,
 (13) -O-CH₂-phenyl, wherein the phenyl group may be
 unsubstituted or substituted with 1 to four substituents
 15 independently selected from:
 (a) -F, -Cl, or -Br,
 (b) -CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 (d) -CF₃,
 20 (e) -CN,
 (f) hydroxy,
 (g) -C₀₋₆ alkyl-N(R⁷)₂, ,
 (14) -O-CH₃,
 (15) -OCH₂CH₃,
 25 (16) -OCH₂CF₃,
 (17) -OCF₃,
 (18) -OCH(CH₃)₂,
 (19) -C(O)CH₂C(O)C(O)OH,
 (20) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
 30 (21) -O-CH₂CH₂ N(CH₃)₂,
 (22) -O-CH(CH₃)CH₂N(CH₃)₂,
 (23) -O-CH₂CH₂ NH₂,
 (24) -O-CH(CH₃)CH₂NH₂,
 (25) -S-CH₃,

- (26) $-C(O)CH_2C(O)C(O)OH$,
- (27) $-CH_2-CH(OH)-CH_2-O-R^7$, and
- (28) $-C(OH)(CH_3)-CH_2N(R^4)(R^5)$.

In another embodiment of the present invention, R^1 is
 5 selected from:

- (1) $-H$,
- (2) $-phenyl$,
- (3) substituted phenyl substituted with 1 or 2 substituents
 independently selected from:
- 10 (a) halo, selected from $-F$, $-Br$, $-Cl$,
- (b) methyl, and
- (c) methoxy,
- (4) phenyl C_{1-3} alkyl-,
- (5) $-O-R^6$,
- 15 (6) $-O-CH_3$, and
- (7) $-C(O)CH_2C(O)C(O)OR^7$.

In one embodiment of the present invention, R^2 is selected
 from:

- (1) $-H$,
- 20 (2) $-R^3$,
- (3) $-C_{1-6}$ alkyl,
- (4) $-C_{1-6}$ alkyl substituted with R^3 , wherein one or more of the
 hydrogen atoms on C_{1-6} alkyl may be replaced with a
 fluorine atom,
- 25 (5) $-O-R^6$,
- (6) $-S-R^6$,
- (7) $-O-C_{1-6}$ alkyl- SR^6 ;
- (8) $-C_{1-6}$ alkyl $(OR^6)(R^4)$,
- (9) $-C_{0-6}$ alkyl- $N(R^4)(R^6)$,
- 30 (10) $-C_{1-6}$ alkyl- $S-R^6$,
- (11) $-C_{0-6}$ alkyl- $C(O)-R^6$,
- (12) $-C_{0-6}$ alkyl- $C(O)CH_2-C(O)-OH$,
- (13) $-C_{1-6}$ alkyl $NR^4C(O)-R^6$,
- (14) $-C_{1-6}$ alkyl- $C(O)N(R^4)(R^5)$, and

(15) $-\text{CH}_2(\text{OR}^7)-\text{R}^6$.

In another embodiment of the present invention, R^2 is selected from:

- (1) $-\text{H}$,
- 5 (2) $-\text{R}^3$,
- (3) $-\text{CH}_3$,
- (4) $-\text{C}_{1-6}$ alkyl substituted with R^3 , wherein one or more of the hydrogen atoms on C_{1-6} alkyl may be replaced with a fluorine atom,
- 10 (5) $-\text{O}-\text{R}^6$,
- (6) $-\text{S}-\text{R}^6$,
- (7) $-\text{O}-\text{C}_{1-6}$ alkyl- SR^6 ;
- (8) $-\text{C}_{1-6}$ alkyl $(\text{OR}^6)(\text{R}^4)$,
- (9) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^4)(\text{R}^6)$,
- 15 (10) $-\text{C}_{0-6}$ alkyl $\text{C}(\text{O})-\text{R}^6$,
- (11) $-\text{C}_{0-6}$ alkyl $\text{C}(\text{O})\text{CH}_2-\text{C}(\text{O})-\text{OH}$,
- (12) $-\text{C}_{1-6}$ alkyl $\text{NR}^4\text{C}(\text{O})-\text{R}^6$,
- (13) $-\text{C}_{1-6}$ alkyl- $\text{C}(\text{O})\text{N}(\text{R}^4)(\text{R}^5)$, and
- (14) $-\text{CH}_2(\text{OR}^7)-\text{R}^6$.

20 In yet another embodiment of the present invention, R^2 is selected from:

- (1) $-\text{H}$,
- (2) $-\text{R}^3$,
- (3) $-\text{CH}_2-\text{R}^3$,
- 25 (4) $-\text{CH}_2\text{CH}_2-\text{R}^3$,
- (5) $-\text{CF}_2-\text{R}^3$,
- (6) $-\text{CH}(\text{CH}_3)-\text{R}^3$,
- (7) $-\text{O}-\text{R}^6$,
- (8) $-\text{S}-\text{phenyl}$,
- 30 (9) $-\text{C}_{1-6}$ alkyl $(\text{OR}^6)(\text{R}^4)$,
- (10) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^4)(\text{R}^6)$,
- (11) $-\text{C}(\text{O})-\text{R}^3$,
- (12) $-\text{C}_{0-6}$ alkyl $\text{C}(\text{O})\text{CH}_2-\text{C}(\text{O})-\text{OH}$,
- (13) $-\text{C}_{1-6}$ alkyl $\text{NR}^4\text{C}(\text{O})-\text{R}^6$,

(14) $-\text{CH}(\text{OCH}_3)\text{R}^3$, and

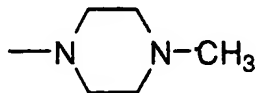
(15) $-\text{CH}(\text{OH})\text{R}^3$.

In another embodiment of the present invention, R^2 is selected from:

- 5 (1) $-\text{R}^3$,
- (2) $-\text{C}_{1-6}$ alkyl substituted with R^3 ,
- (3) $-\text{O}-\text{R}^6$,
- (4) $-\text{S}(\text{O})_n-\text{R}^6$,
- (5) $-\text{C}_{1-6}$ alkyl $(\text{OR}^6)(\text{R}^4)$,
- 10 (6) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^4)(\text{R}^6)$, and
- (7) $-\text{C}_{1-6}$ alkyl- $\text{C}(\text{O})\text{N}(\text{R}^4)(\text{R}^5)$.

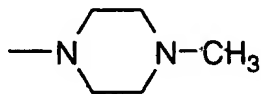
In one embodiment of the present invention, R^3 is selected from:

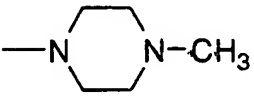
- (1) phenyl;
- 15 (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
 - (a) halogen,
 - (b) C_{1-6} alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - 20 (c) C_{1-6} alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - (e) $-\text{S}-\text{C}_{1-6}$ alkyl,
 - (f) $-\text{CN}$,
 - 25 (g) hydroxy,
 - (h) phenyloxy,
 - (i) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^7)_2$,
 - (j)

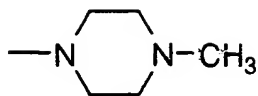


- 30 (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,

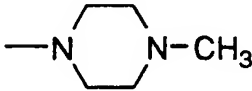
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;
- (3) thienyl,
- 5 (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - 10 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - 15 (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)


*N1CCN(C)CC1
 - 20 (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - 25 (iii) -CF₃, and
 - (iv) hydroxy;
 - (5) pyridyl,
 - (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
 - 30 (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,

- 5
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)
- 10
- 
- (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- 15
- (7) imidazolyl,
 - (8) substituted imidazolyl substituted on-carbon with one or two substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)
- 20
- 25
- 30



- (k) oxo, and
- (l) substituted phenoxy with 1, 2, or 3 substituents selected from:
- 5 (i) halogen,
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;
- (9) pyrrolyl,
- 10 (10) substituted pyrrolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 15 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- 20 (g) hydroxy,
- (h) phenoxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,
- (j)
-
- 25 (k) oxo, and
- (l) substituted phenoxy with 1, 2, or 3 substituents selected from:
- (i) halogen,
- (ii) C₁₋₆ alkyl,
- 30 (iii) -CF₃, and
- (iv) hydroxy;

- (11) pyrazolyl,
- (12) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
 - 5 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - 10 (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - 15 (j)
- 
- (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - 20 (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- (15) piperidinyl,
- 25 (16) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - 30 (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O,

- (h) benzyl, and
- (i) hydroxy;
- (17) morpholinyl,
- (18) substituted morpholinyl substituted at a carbon or nitrogen
5 atom with 1 or 2 substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - 10 (e) -OCF₃,
 - (f) -CN,
 - (g) =O,
 - (h) benzyl, and
 - (i) hydroxy;
- 15 (19) hexahydrothieno[3,4-d]imidazolyl,
- (20) substituted hexahydrothieno[3,4-d] substituted
hexahydrothieno[3,4-d]imidazolyl with one or two
substituents independently selected from:
 - (a) oxo,
 - 20 (b) halogen,
 - (c) C₁₋₆ alkyl,
 - (d) C₁₋₆ alkyloxy-,
 - (e) -CF₃,
 - (f) -OCF₃,
 - 25 (g) -CN, and
 - (h) hydroxy,
- (21) naphthyl,
- (22) substituted naphthyl with 1, 2, or 3 substituents
independently selected from:
 - 30 (a) -halogen,
 - (b) -C₁₋₆ alkyl,
 - (c) -C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - 35 (f) -CN, and

- (g) -hydroxy,
- (23) indolyl,
- (24) substituted indolyl substituted on a carbon atom with one or two substituents independently selected from:
- 5 (a) -halogen,
- (b) -C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- (e) -OCF₃,
- 10 (f) -CN, and
- (g) -hydroxy;
- (25) C₃₋₆ cycloalkyl fused with a phenyl ring;
- (26) substituted C₃₋₆ cycloalkyl fused with a phenyl ring substituted on carbon with one or two substituents independently selected from:
- 15 (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- 20 (e) -OCF₃,
- (f) -CN,
- (g) =O, and
- (h) hydroxy;
- (27) pyrazinyl;
- 25 (28) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 30 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- 35 (g) hydroxy,

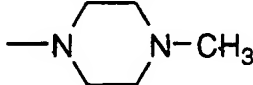
- (h) phenyloxy,
 (i) -C₀₋₆ alkyl-N(R⁷)₂,

$$\text{---N} \begin{array}{c} \diagup \quad \diagdown \\ | \quad | \\ \diagdown \quad \diagup \end{array} \text{N-CH}_3$$

 (j) ,
 (k) oxo, and
 5 (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 10 (iv) hydroxy;
 (29) pyrimidinyl;
 (30) substituted pyrimidinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
 15 (a) halogen,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 20 (d) phenyl,
 (e) -S-C₁₋₆ alkyl,
 (f) -CN,
 (g) hydroxy,
 (h) phenyloxy,
 (i) -C₀₋₆ alkyl-N(R⁷)₂,

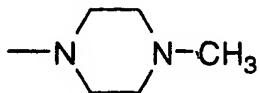
$$\text{---N} \begin{array}{c} \diagup \quad \diagdown \\ | \quad | \\ \diagdown \quad \diagup \end{array} \text{N-CH}_3$$

 25 (j) ,
 (k) oxo, and
 (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 (i) halogen,
 30 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;

- (31) triazolyl;
- (32) substituted triazolyl with one or two substituents independently selected from:
- (a) halogen,
 - 5 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - 10 (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - 15 (j) ,

CN1CCCCC1
 - (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - 20 (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- (33) tetrazolyl;
- (34) substituted tetrazolyl with a substituent selected from:
- 25 (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - 30 (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,

- (h) phenyloxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,



- (j) ,
- (k) oxo, and
- 5 (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - 10 (iv) hydroxy;
- (35) C₃₋₆ cycloalkyl;
- (36) substituted C₃₋₆ cycloalkyl substituted with one or two substituents independently selected from:
 - (a) halogen,
 - 15 (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - 20 (g) =O,
 - (h) benzyl, and
 - (i) hydroxy;
- (37) tetrahydrofuran;
- (38) substituted tetrahydrofuran substituted with one or two substituents independently selected from:
 - 25 (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - 30 (e) -OCF₃,
 - (f) -CN,
 - (g) =O,
 - (h) benzyl, and

- (i) hydroxy;
- (39) piperazinyl;
- (40) substituted piperazinyl substituted with one or two substituents independently selected from:
- 5 (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- (e) -OCF₃,
- 10 (f) -CN,
- (g) =O,
- (h) benzyl, and
- (i) hydroxy;
- (41) benzotriazolyl,
- 15 (42) substituted benzotriazolyl substituted on a carbon atom with one or two substituents independently selected from:
- (a) -halogen,
- (b) -C₁₋₆ alkyl,
- (c) -C₁₋₆ alkyloxy-,
- 20 (d) -CF₃,
- (e) -OCF₃,
- (f) -CN, and
- (g) -hydroxy;
- (43) benzoimidazolyl,
- 25 (44) substituted benzoimidazolyl substituted on a carbon atom with one or two substituents independently selected from:
- (a) -halogen,
- (b) -C₁₋₆ alkyl,
- (c) -C₁₋₆ alkyloxy-,
- 30 (d) -CF₃,
- (e) -OCF₃,
- (f) -CN, and
- (g) -hydroxy.

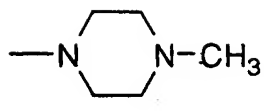
In another embodiment of the present invention, R³ is
35 selected from:

- (1) phenyl;
- (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
- 5 (a) halogen, selected from -F, -Cl, -Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,-,
- (d) -CN,
- 10 (e) hydroxy, and
- (f) oxo;
- (3) thienyl,
- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
- 15 (a) halogen, selected from F, Cl, and Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- 20 (5) pyridyl,
- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
- 25 atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) hydroxy, and
- (e) oxo;
- 30 (7) imidazolyl,
- (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- 35 (a) halogen, selected from -F, -Cl, and -Br;

- (b) -CH₃,
(c) -CF₃,
(d) -OCH₃,
(e) -OCF₃, and
5 (f) hydroxy;
(11) C₃-6 cycloalkyl,
(12) substituted C₃-6 cycloalkyl with 1 or 2 substituents
independently selected from:
(a) halogen, selected from -F, -Cl, and -Br,
10 (b) CH₃,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
15 (g) =O, and
(h) hydroxy;
(13) piperidinyl,
(14) substituted piperidinyl substituted on carbon with one or
two substituents independently selected from:
20 (a) halogen selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
25 (f) =O, and
(g) hydroxy;
(15) morpholinyl,
(16) substituted morpholinyl substituted on carbon or nitrogen
with 1 or 2 substituents independently selected from:
30 (a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃, and

- (f) hydroxy;
- (17) hexahydrothieno[3,4-d]imidazolyl,
- (18) naphthyl,
- (19) substituted naphthyl with 1, 2, or 3 substituents independently selected from:
- (a) -halogen, selected from -F, -Cl, and -Br,
- (b) methyl,
- (c) methoxy-,
- (d) -CF₃,
- (e) -OCF₃,
- (f) -CN, and
- (g) -hydroxy,
- (20) indolyl,
- (21) 1,2,3,4-tetrahydronaphthalenyl,
- (22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on carbon with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
- (b) methyl,
- (c) methoxy-,
- (d) -CF₃,
- (e) -OCF₃,
- (f) -CN,
- (g) =O, and
- (h) hydroxy;
- (23) pyrazinyl;
- (24) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) hydroxy,
- (e) phenyloxy,
- (f) -C₀₋₆ alkyl-N(R⁷)₂, and

(g)



- 5 (25) pyrimidinyl;
(26) substituted pyrimidinyl substituted on nitrogen or carbon
with a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-, and
10 (d) phenyl,
(27) triazolyl;
(28) substituted triazolyl with a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
15 (c) methoxy-, and
(d) hydroxy,
(29) tetrazolyl;
(30) substituted tetrazolyl with a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
20 (b) methyl,
(c) methoxy-, and
(d) hydroxy,
(31) C₃₋₆ cycloalkyl;
(32) substituted C₃₋₆ cycloalkyl substituted with one or two
25 substituents independently selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃, and
30 (e) -OCF₃,
(33) tetrahydrofuran;
(34) substituted tetrahydrofuran substituted with one or two
substituents independently selected from:

- 5 (a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃, and
(e) -OCF₃,
(35) piperazinyl;
(36) substituted piperazinyl substituted with one or two
substituents independently selected from:
10 (a) halogen, selected from -F, -Cl, and -Br,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) benzyl, and
15 (g) hydroxy;
(37) benzotriazolyl,
(38) substituted benzotriazolyl substituted on carbon with one or
two substituents independently selected from:
20 (a) -halogen, selected from -F, -Cl, and -Br,
(b) -methyl,
(c) methoxy-,
(d) -CF₃, and
(e) -OCF₃,
(39) benzoimidazolyl, and
25 (40) substituted benzoimidazolyl substituted on carbon with one
or two substituents independently selected from:
(a) -halogen, selected from -F, -Cl, and -Br,
(b) -methyl,
(c) methoxy-,
30 (d) -CF₃, and
(e) -OCF₃.

In yet another embodiment of the present invention, each
R³ is independently selected from:

- (1) phenyl,

- (2) substituted phenyl with 1, 2, or 3 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, -Br,
 - (b) -CH₃,
 - 5 (c) methyloxy-,
 - (d) ethyloxy-,
 - (e) -OCH₂CF₃,
 - (f) -OCF₂CH₃,
 - (g) -CF₃,
 - 10 (h) -CH₂CF₃,
 - (i) -CF₂CH₃,
 - (j) -OCF₃,
 - (k) -CN, and
 - (l) hydroxy;
 - 15 (3) thienyl,
 - (4) substituted thienyl substituted on a carbon atom with a substituent selected from:
 - (a) F,
 - (b) Cl, and
 - 20 (c) methyl;
 - (5) pyridyl,
 - (6) substituted pyridyl substituted on a carbon with a substituent selected from:
 - (a) -F,
 - 25 (b) -Cl,
 - (c) -CH₃,
 - (d) -CF₃,
 - (e) -OCH₃,
 - (f) -OCF₃,
 - 30 (g) hydroxy, and
 - (h) oxo;
 - (7) pyrazolyl
 - (8) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
 - 35 (a) -F,

- (b) -Cl,
 (c) -CH₃, and
 (d) -CF₃;
- (9) C₃-6 cycloalkyl,
- 5 (10) piperidinyl,
 (11) substituted piperidinyl substituted on carbon with a
 substituent selected from:
 (a) methoxy-,
 (b) -OCF₃,
 10 (c) =O, and
 (d) hydroxy;
- (12) morpholinyl,
 (13) naphthyl,
 (14) 1,2,3,4-tetrahydronaphthalenyl,
- 15 (15) pyrazinyl;
 (16) substituted pyrazinyl substituted on nitrogen or carbon with
 a substituent selected from:
 (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 20 (c) -CF₃,
 (d) methoxy-,
 (e) -N(CH₃)₂, and
 (f)
- *N1CCN(C)CC1
- 25 (17) pyrimidinyl,
 (18) [1,2,3]-triazolyl,
 (19) [1,2,4]-triazolyl,
 (20) tetrazolyl;
 (21) cyclopropyl,
 30 (22) cyclobutyl,
 (23) cyclopentyl,
 (24) cyclohexyl,
 (25) tetrahydrofuran,

- (26) piperazinyl;
(27) substituted piperazinyl substituted with a substituent
selected from:
(a) -F,
5 (b) -Cl,
(c) methyl,
(d) -CF₃, and
(e) benzyl,
(28) benzotriazolyl, and
10 (29) benzoimidazolyl.

In still another embodiment of the present invention, R³ is
selected from:

- (1) phenyl;
(2) substituted phenyl with 1, 2, or 3 substituents independently
15 selected from:
(a) halogen, selected from -F, -Cl, -Br,
(b) -CH₃,
(c) methyloxy-,
(d) phenyl,
20 (e) -CF₃,
(f) -OCF₃,
(g) -CN,
(h) hydroxy,
(i) phenyloxy, and
25 (j) substituted phenyloxy with 1, 2, or 3 substituents
selected from:
(i) halogen, selected from -F, -Cl, -Br,
(ii) -CH₃,
(iii) -CF₃, and
30 (iv) hydroxy.

In one embodiment of the present invention, each R⁴ is
independently selected from:

- (1) -H,
(2) -C₁₋₄ alkyl,
35 (3) -CF₃,

- (4) -R³,
(5) -C₂₋₃ alkenyl,
(6) -C₁₋₃ alkyl-R³,
(7) -C₂₋₃ alkenyl-R³, and
5 (8) -C(O)-R³.

In another embodiment of the present invention, each R⁴ is independently selected from:

- (1) -H,
(2) -C₁₋₄ alkyl,
10 (3) -CF₃,
(4) -R³,
(5) -C₁₋₃ alkyl-R³, and
(6) -C(O)-R³.

In one embodiment of the present invention, each R⁵ is
15 independently selected from:

- (1) -H,
(2) -C₁₋₃ alkyl,
(3) -CF₃,
(4) -R³,
20 (5) -C₂₋₃ alkenyl,
(6) -C₁₋₃ alkyl-R³,
(7) -S(O)_n-R³,
(8) -C(O)-R³,
(9) -C(O)OR⁴, and
25 (10) -C(O)C(O)OH;

In another embodiment of the present invention, each R⁵ is independently selected from:

- (1) -H,
(2) -C₁₋₃ alkyl,
30 (3) -CF₃,
(4) -R³,
(5) -C₁₋₃ alkyl-R³,
(6) -C(O)-R³,
(7) -C(O)OR⁴, and

(8) $-\text{C}(\text{O})\text{C}(\text{O})\text{OH}$.

In another embodiment of the present invention, each R^5 is independently selected from:

- (1) $-\text{H}$,
- 5 (2) $-\text{CH}_3$,
- (3) $-\text{CF}_3$,
- (4) phenyl,
- (5) $-\text{benzyl}$,
- (6) $-\text{C}(\text{O})\text{OR}^4$, and
- 10 (7) $-\text{C}(\text{O})\text{C}(\text{O})\text{OH}$;

In one embodiment of the present invention, R^7 is independently selected from H , and $-\text{C}_{1-6}$ alkyl.

In one embodiment of the present invention, R^8 is selected from hydrogen, methyl and $-\text{O}-\text{C}_{1-6}$ alkyl.

15 In yet another embodiment of the present invention, R^8 is hydrogen.

In one embodiment of the present invention, R^9 is selected from:

- (1) $-\text{H}$,
- 20 (2) $-\text{O}-\text{C}_{1-3}$ alkyl,
- (3) $-\text{OH}$, and
- (4) oxo.

Also included within the present invention are pharmaceutical compositions useful for inhibiting HIV integrase, comprising an effective amount of a compound of this invention, and a pharmaceutically acceptable carrier. Pharmaceutical compositions useful for treating infection by HIV, or for treating AIDS or ARC, are also encompassed by the present invention, as well as a method of inhibiting HIV integrase, and a method of treating infection by HIV, or of treating AIDS or ARC. Additionally, the present invention is directed to a pharmaceutical composition comprising a therapeutically effective amount of a compound of the present invention in combination with a therapeutically effective amount of an AIDS treatment agent selected from:

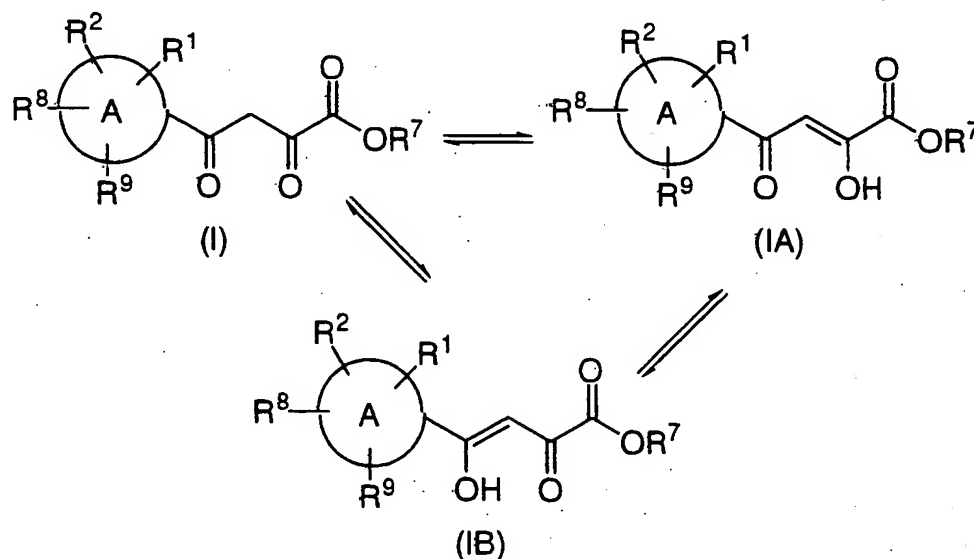
- 35 (1) an AIDS antiviral agent,

(2) an anti-infective agent, and

(3) an immunomodulator.

The compounds of the present invention may have asymmetric centers and may occur, except when specifically noted, as mixtures of stereoisomers or as individual diastereomers, or enantiomers, with all isomeric forms being included in the present invention.

As is recognized by one of ordinary skill in the art, the diketo-acid/ester compounds of the present invention exist as tautomers, and thus by using the phrase "and tautomers thereof" in describing compounds of structural formula (I), Applicants also intend the following tautomeric forms of the same compound (IA) and (IB):



By naming or referring to compound (I) and tautomers thereof, it is understood for the purposes of the present application that the tautomers (IA) and (IB) are also intended. Similarly, by referring to compound (IA), it is understood for the purposes of the present application that the tautomers (I) and (IB) are also intended. The same holds true for references to tautomer (IB).

When any variable (e.g., R³, R⁴, etc.) occurs more than one time in any constituent or in formula I, its definition on each occurrence is independent of its definition at every other occurrence. Also,

combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

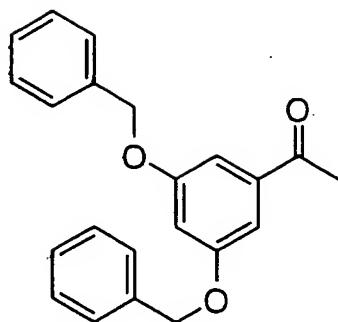
The compounds of the present inventions are useful in the inhibition of HIV integrase, the prevention or treatment of infection by human immunodeficiency virus (HIV) and the treatment of consequent pathological conditions such as AIDS. Treating AIDS or preventing or treating infection by HIV is defined as including, but not limited to, treating a wide range of states of HIV infection: AIDS, ARC (AIDS related complex), both symptomatic and asymptomatic, and actual or potential exposure to HIV. For example, the compounds of this invention are useful in treating infection by HIV after suspected past exposure to HIV by e.g., blood transfusion, exchange of body fluids, bites, accidental needle stick, or exposure to patient blood during surgery.

The compounds of this invention are useful in the preparation and execution of screening assays for antiviral compounds. For example, the compounds of this invention are useful for isolating enzyme mutants, which are excellent screening tools for more powerful antiviral compounds. Furthermore, the compounds of this invention are useful in establishing or determining the binding site of other antivirals to HIV integrase, e.g., by competitive inhibition. Thus the compounds of this invention are commercial products to be sold for these purposes.

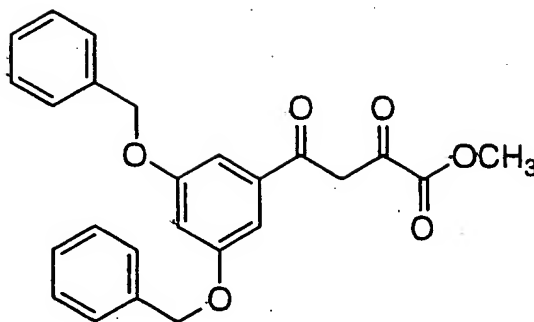
The present invention also provides for the use of a compound of structural formula (I) to make a pharmaceutical composition useful for inhibiting HIV integrase and in the treatment of AIDS or ARC.

Schemes AI, AII, and AVI illustrate the preparation of compounds wherein A is di-aryloxy/alkyloxy substituted phenyl. Scheme AIII illustrates the preparation of the compounds of the present invention wherein A is arylalkyl substituted phenyl. Schemes AIV and AV describe the synthesis of compounds wherein A is amino substituted phenyl. Scheme AVII describes the synthesis of compounds wherein A is indolyl. Scheme IX illustrates the synthesis of pyridyl compounds.

Scheme AI

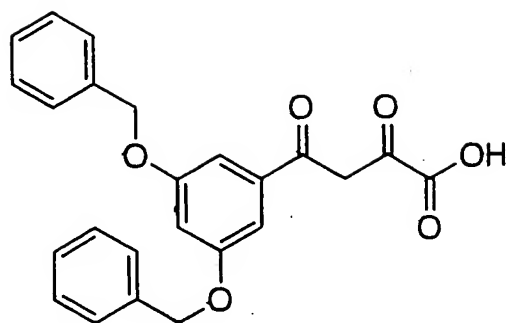
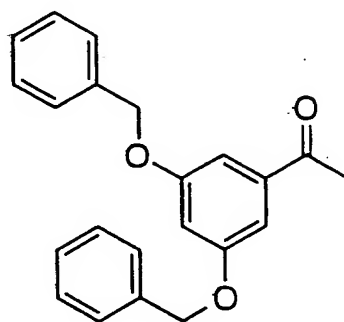


NaH
DME
Dimethyl oxalate

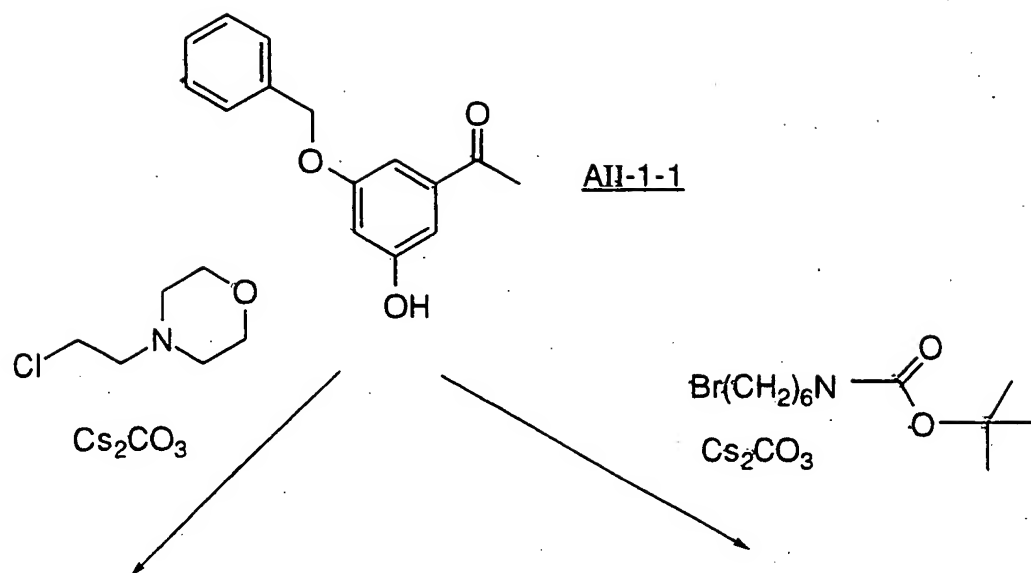


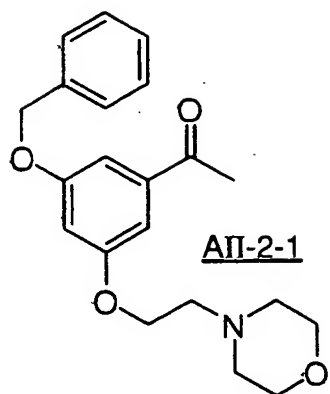
AI-1-1

1 N NaOH
THF/MeOH 1:1

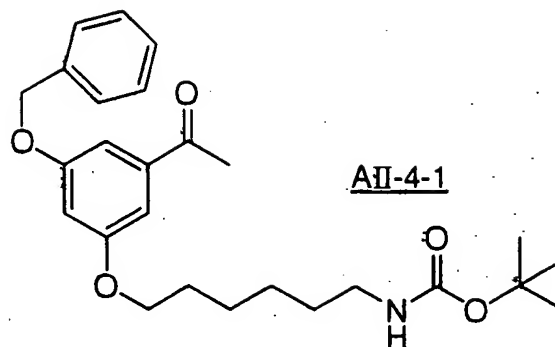
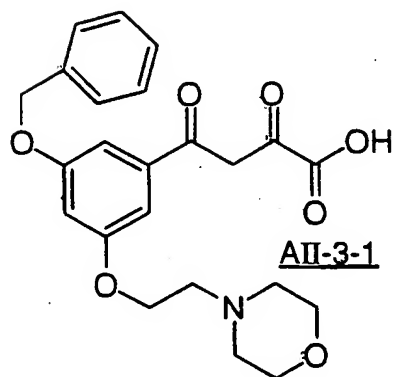
AI-2-1**Scheme AII**

H₂ / Pd / C
EtOH / Et₂O

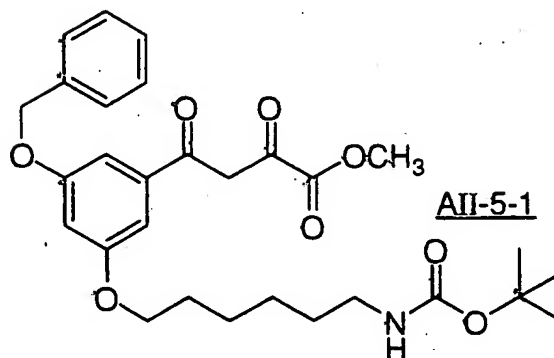




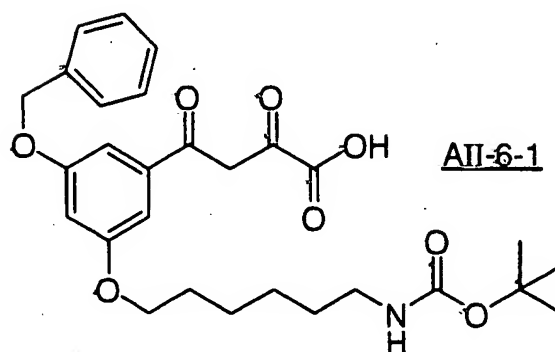
1) NaH
DME
dimethyl oxalate
2) NaOH



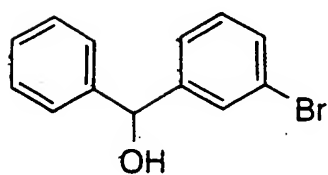
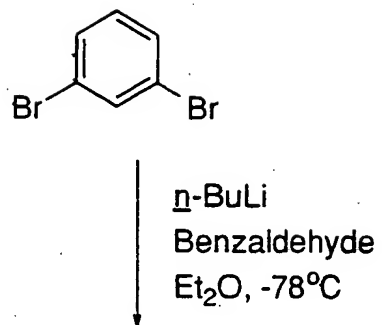
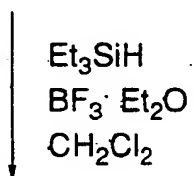
NaH
DME
dimethyl oxalate

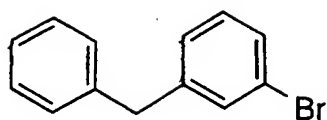
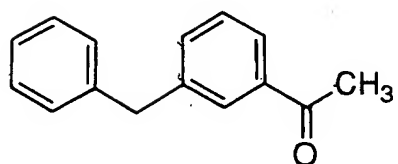
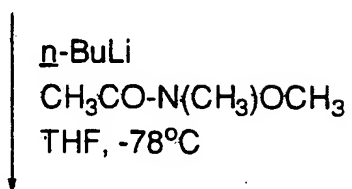
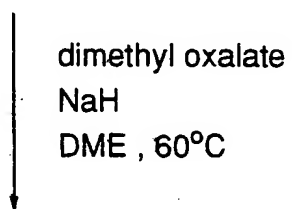


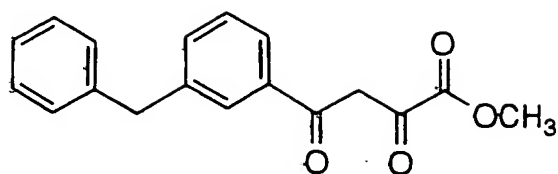
NaOH



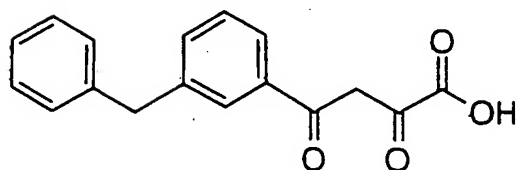
Scheme AIII

AIII-1-1

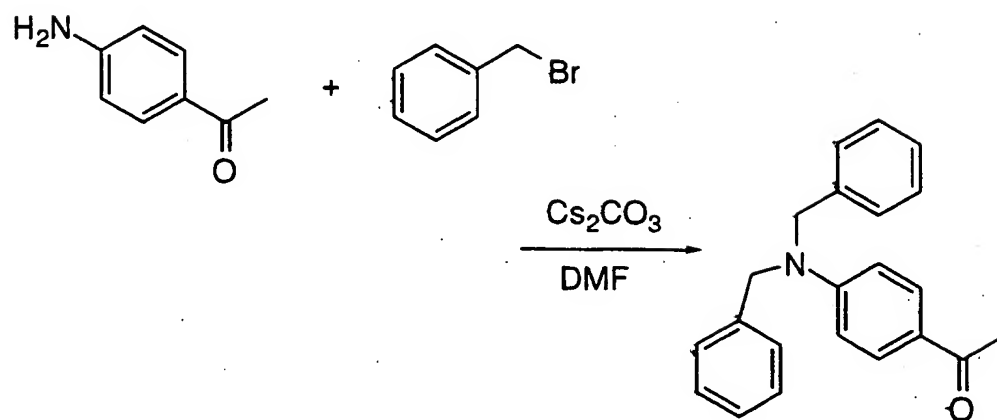
AIII-2-1AIII-3-1

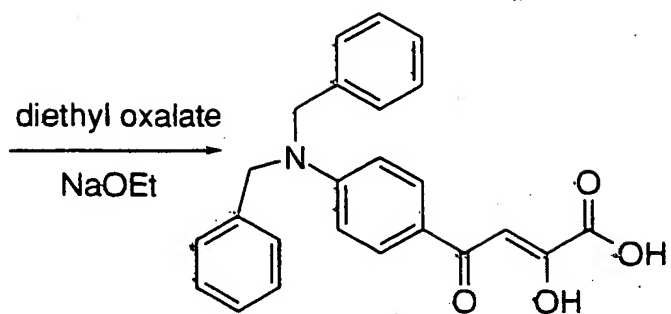
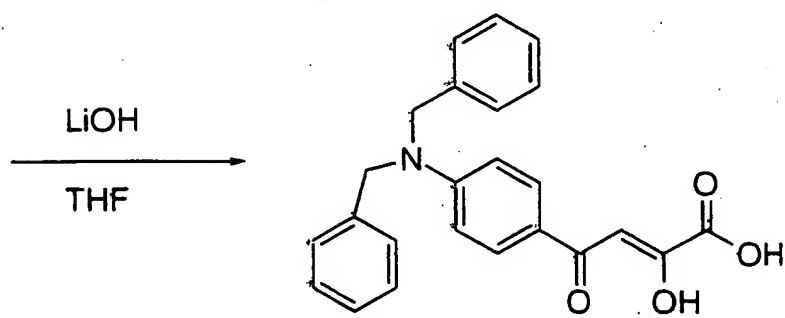
AIII-4-1

NaOH
THF / MeOH / H₂O

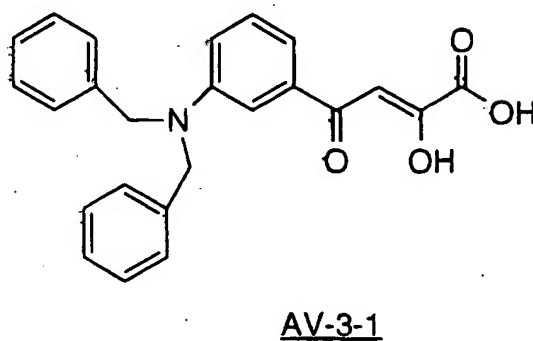
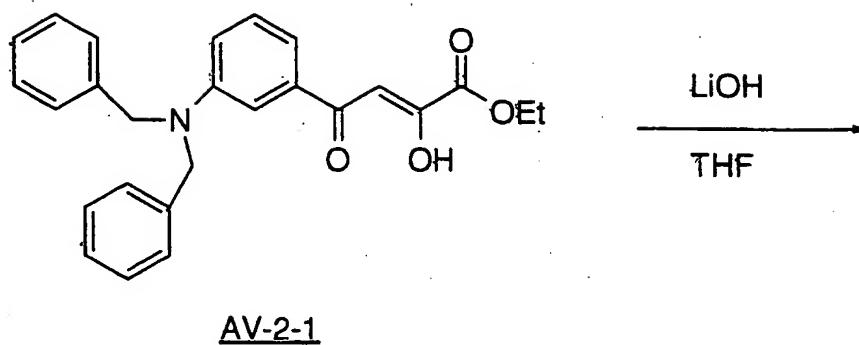
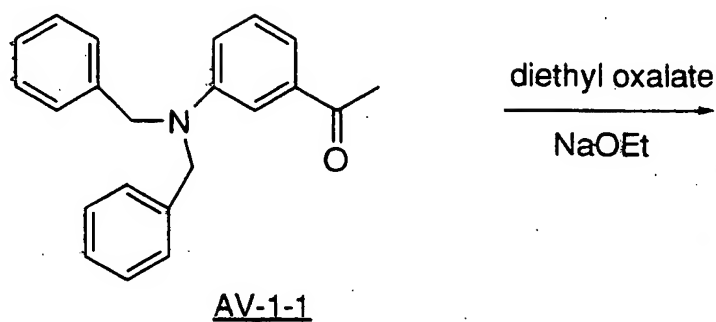
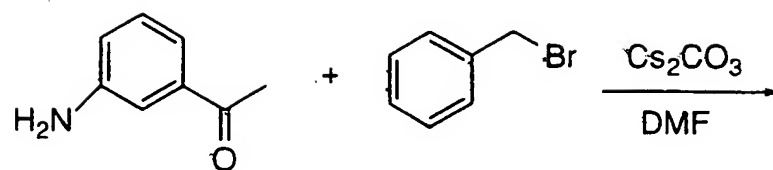
AIII-5-1

Scheme A-IV

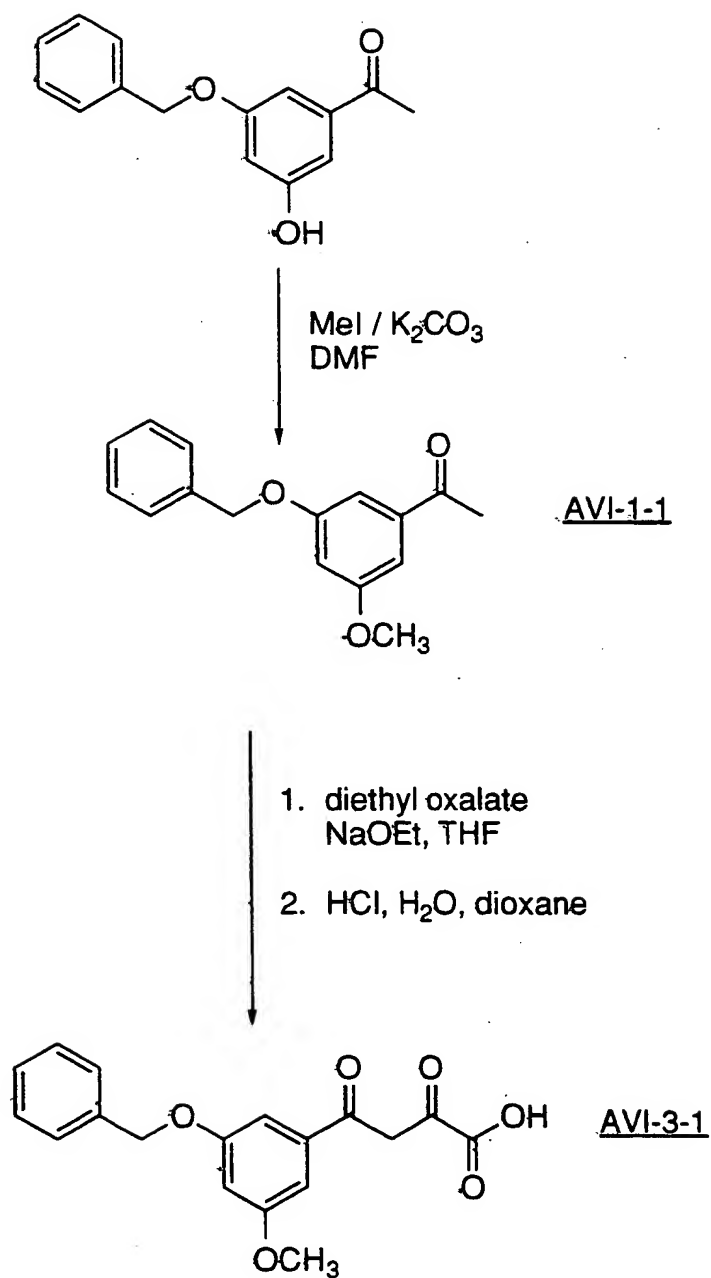
AIV-1-1

AIV-2-1AIV-3-1

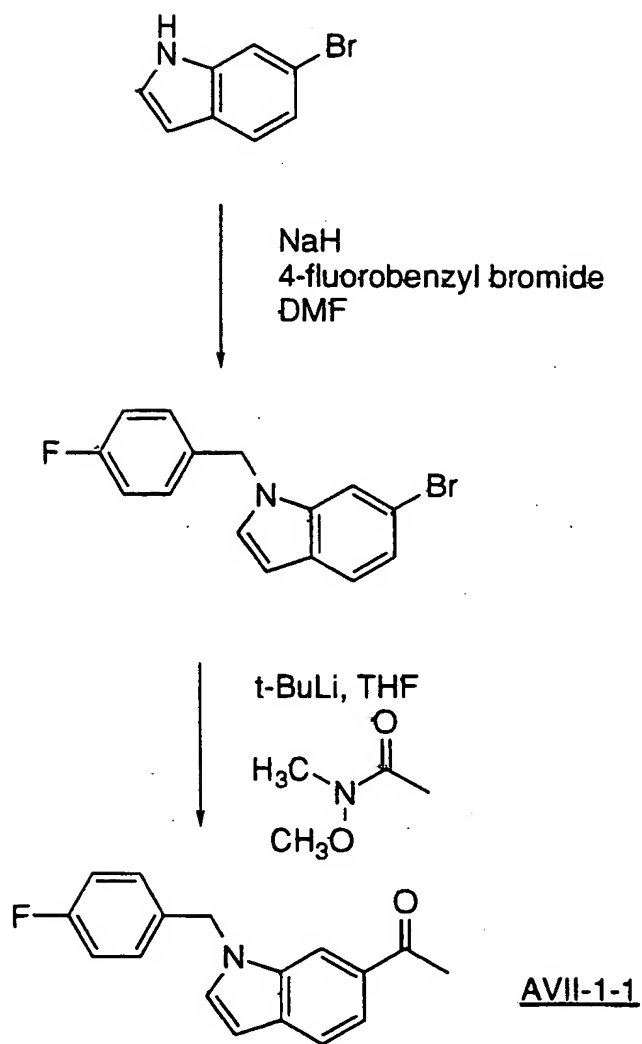
Scheme A-V

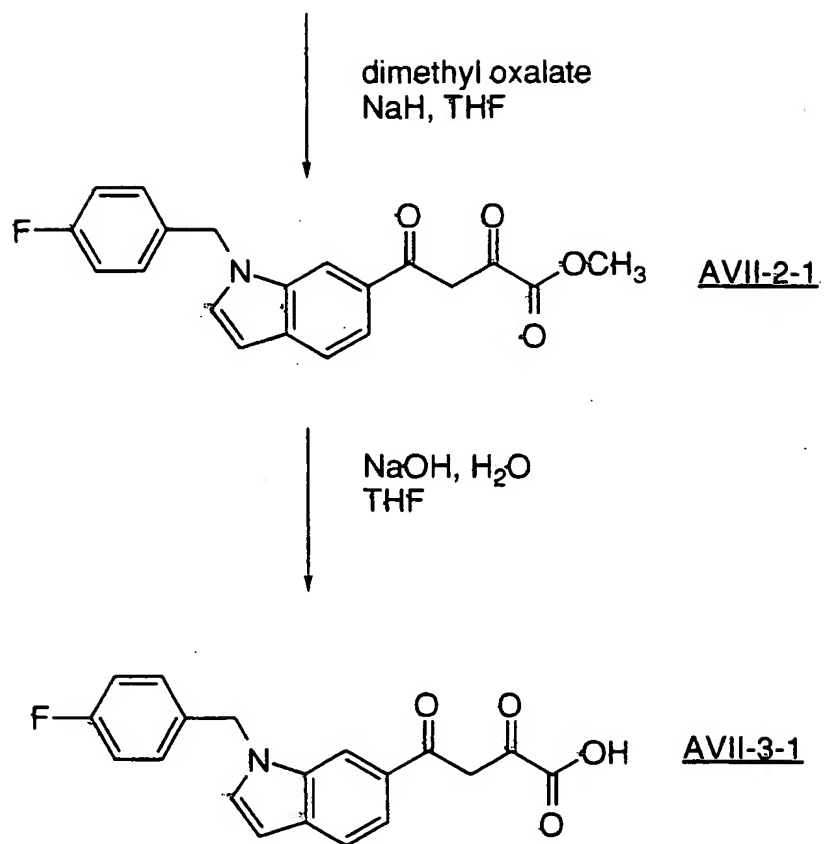


Scheme AVI

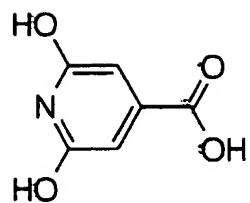


Scheme AVII

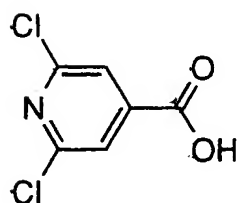




Scheme IX

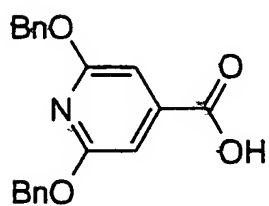


i. POCl_3 , 200°C , sealed tube
ii. H_2O

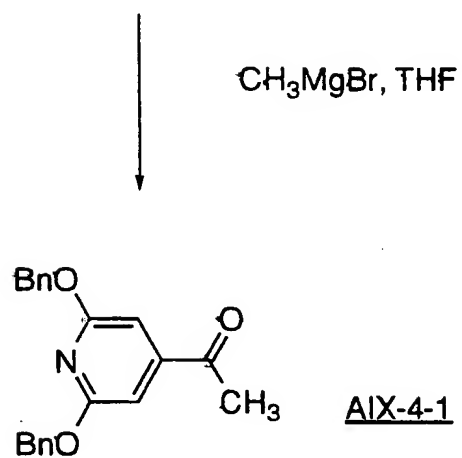
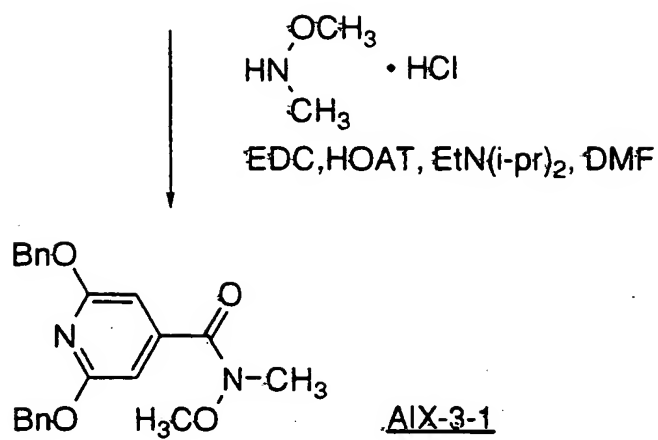


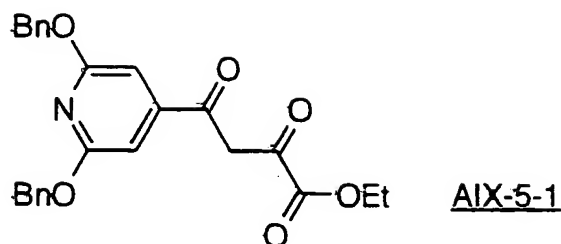
AIX-1-1

$\text{BnO}^- \text{Na}^+$, DMF, reflux

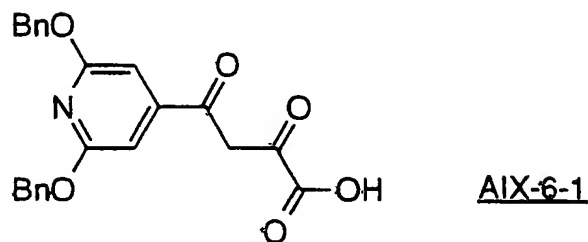


AIX-2-1





i. Aq NaOH, EtOH
ii. Aq HCl



The compounds of the present invention may be administered in the form of pharmaceutically acceptable salts. The term "pharmaceutically acceptable salt" is intended to include all acceptable salts such as acetate, lactobionate, benzenesulfonate, laurate, benzoate, malate, bicarbonate, maleate, bisulfate, mandelate, bitartrate, mesylate, borate, methylbromide, bromide, methylnitrate, calcium edetate, methylsulfate, camsylate, mucate, carbonate, napsylate, chloride, nitrate, clavulanate, N-methylglucamine, citrate, ammonium salt, dihydrochloride, oleate, edetate, oxalate, edisylate, pamoate (embonate), estolate, palmitate, esylate, pantothenate, fumarate, phosphate/diphosphate, gluceptate, polygalacturonate, gluconate, salicylate, glutamate, stearate, glycolylarsanilate, sulfate, hexylresorcinate, subacetate, hydrabamine, succinate, hydrobromide, tannate, hydrochloride, tartrate, hydroxynaphthoate, teoclate, iodide, tosylate, isothionate, triethiodide, lactate, panoate, valerate, and the like which can be used as a dosage form for modifying the solubility or hydrolysis characteristics or can be used in sustained release or pro-

drug formulations. Depending on the particular functionality of the compound of the present invention, pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glutamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chlorprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide. These salts may be prepared by standard procedures, e.g. by reacting a free acid with a suitable organic or inorganic base. Where a basic group is present, such as amino, an acidic salt, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

Also, in the case of an acid (-COOH) or alcohol group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

For these purposes, the compounds of the present invention may be administered orally, parenterally (including subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques), by inhalation spray, or rectally, in dosage unit formulations containing conventional non-toxic pharmaceutically-acceptable carriers, adjuvants and vehicles.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

Thus, in accordance with the present invention there is further provided a method of treating and a pharmaceutical composition for treating HIV infection and AIDS. The treatment involves administering to a patient in need of such treatment a pharmaceutical composition comprising a pharmaceutical carrier and a therapeutically-effective amount of a compound of the present invention.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

These pharmaceutical compositions may be in the form of orally-administrable suspensions or tablets, nasal sprays, sterile injectible preparations, for example, as sterile injectible aqueous or oleagenous suspensions or suppositories.

When administered orally as a suspension, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may contain microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners/flavoring agents known in the art. As immediate release tablets, these compositions may contain microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants known in the art.

When administered by nasal aerosol or inhalation, these compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The injectible solutions or suspensions may be formulated according to known art, using suitable non-toxic, parenterally-acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution or isotonic sodium chloride solution, or suitable dispersing or wetting and suspending agents, such as sterile, bland, fixed oils, including synthetic mono- or diglycerides, and fatty acids, including oleic acid.

When rectally administered in the form of suppositories, these compositions may be prepared by mixing the drug with a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters of polyethylene glycols, which are solid at ordinary temperatures, but
5 liquefy and/or dissolve in the rectal cavity to release the drug.

The compounds of this invention can be administered orally to humans in a dosage range of 1 to 1000 mg/kg body weight in divided doses. One preferred dosage range is 0.1 to 200 mg/kg body weight orally in divided doses. Another preferred dosage range is 0.5 to 100 mg/kg
10 body weight orally in divided doses. For oral administration, the compositions are preferably provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient
15 for the symptomatic adjustment of the dosage to the patient to be treated. It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound,
20 the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

The present invention is also directed to combinations of the HIV integrase inhibitor compounds with one or more agents useful in
25 the treatment of AIDS. For example, the compounds of this invention may be effectively administered, whether at periods of pre-exposure and/or post-exposure, in combination with effective amounts of the AIDS antivirals, immunomodulators, antiinfectives, or vaccines, such as those in the following table.

ANTIVIRALS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
097	Hoechst/Bayer	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase (RT) inhibitor)
Amprenivir 141 W94 GW 141	Glaxo Wellcome	HIV infection, AIDS, ARC (protease inhibitor)
Abacavir (1592U89) GW 1592	Glaxo Wellcome	HIV infection, AIDS, ARC (RT inhibitor)
Acemannan	Carrington Labs (Irving, TX)	ARC
Acyclovir	Burroughs Wellcome	HIV infection, AIDS, ARC, in combination with AZT
AD-439	Tanox Biosystems	HIV infection, AIDS, ARC
AD-519	Tanox Biosystems	HIV infection, AIDS, ARC
Adefovir dipivoxil AL-721	Gilead Sciences Ethigen (Los Angeles, CA)	HIV infection ARC, PGL HIV positive, AIDS
Alpha Interferon	Glaxo Wellcome	Kaposi's sarcoma, HIV in combination w/Retrovir

Ansamycin LM 427	Adria Laboratories (Dublin, OH) Erbamont (Stamford, CT)	ARC
Antibody which neutralizes pH labile alpha aberrant Interferon AR177	Advanced Biotherapy Concepts (Rockville, MD)	AIDS, ARC
beta-fluoro-ddA	Aronex Pharm	HIV infection, AIDS, ARC
BMS-232623 (CGP-73547)	Nat'l Cancer Institute	AIDS-associated diseases
BMS-234475 (CGP-61755)	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
CI-1012 Cidofovir	Bristol-Myers Squibb/ Novartis	HIV infection, AIDS, ARC (protease inhibitor)
Curdlan sulfate Cytomegalovirus immune globin Cytovene Ganciclovir	Warner-Lambert Gilead Science	HIV-1 infection CMV retinitis, herpes, papillomavirus
	AJI Pharma USA MedImmune	HIV infection CMV retinitis
	Syntex	sight threatening CMV peripheral CMV retinitis
Delaviridine	Pharmacia-Upjohn	HIV infection, AIDS, ARC (RT inhibitor)
Dextran Sulfate	Ueno Fine Chem. Ind. Ltd. (Osaka, Japan)	AIDS, ARC, HIV positive asymptomatic

ddC	Hoffman-La Roche	HIV infection, AIDS, ARC
Dideoxycytidine		
ddI	Bristol-Myers Squibb	HIV infection, AIDS, ARC; combination with AZT/d4T
Dideoxyinosine		
DMP-450	AVID (Camden, NJ)	HIV infection, AIDS, ARC (protease inhibitor)
Efavirenz (DMP 266) (-) 6-Chloro-4(S)- cyclopropylethynyl- 4(S)-trifluoro- methyl-1,4-dihydro- 2H-3,1-benzoxazin- 2-one, STOCRINE	DuPont Merck	HIV infection, AIDS, ARC (non-nucleoside RT inhibitor)
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
Famciclovir	Smith Kline	herpes zoster, herpes simplex
FTC	Emory University	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
GS 840	Gilead	HIV infection, AIDS, ARC (reverse transcriptase inhibitor)
HBY097	Hoechst Marion Roussel	HIV infection, AIDS, ARC (non-nucleoside reverse transcriptase inhibitor)

Hypericin	VIMRx Pharm.	HIV infection, AIDS, ARC
Recombinant Human Interferon Beta	Triton Biosciences (Alameda, CA)	AIDS, Kaposi's sarcoma, ARC
Interferon alfa-n3	Interferon Sciences	ARC, AIDS
Indinavir	Merck	HIV infection, AIDS, ARC, asymptomatic HIV positive, also in combination with AZT/ddI/ddC
ISIS 2922	ISIS Pharmaceuticals	CMV retinitis
KNI-272	Nat'l Cancer Institute	HIV-assoc. diseases
Lamivudine, 3TC	Glaxo Wellcome	HIV infection, AIDS, ARC (reverse transcriptase inhibitor); also with AZT
Lobucavir	Bristol-Myers Squibb	CMV infection
Nelfinavir	Agouron Pharmaceuticals	HIV infection, AIDS, ARC (protease inhibitor)
Nevirapine	Boehringer Ingelheim	HIV infection, AIDS, ARC (RT inhibitor)
Novapren	Novaferon Labs, Inc. (Akron, OH)	HIV inhibitor
Peptide T Octapeptide Sequence	Peninsula Labs (Belmont, CA)	AIDS
Trisodium Phosphonoformate	Astra Pharm. Products, Inc	CMV retinitis, HIV infection, other CMV infections

PNU-140690	Pharmacia Upjohn	HIV infection, AIDS, ARC (protease inhibitor)
Probucol	Vyrex	HIV infection, AIDS
RBC-CD4	Sheffield Med. Tech (Houston TX)	HIV infection, AIDS, ARC
Ritonavir	Abbott	HIV infection, AIDS, ARC (protease inhibitor)
Saquinavir	Hoffmann- LaRoche	HIV infection, AIDS, ARC (protease inhibitor)
Stavudine; d4T Didehydrodeoxy- thymidine	Bristol-Myers Squibb	HIV infection, AIDS, ARC
Valaciclovir	Glaxo Wellcome	genital HSV & CMV infections
Virazole	Viratek/ICN	asymptomatic HIV
Ribavirin	(Costa Mesa, CA)	positive, LAS, ARC
VX-478	Vertex	HIV infection, AIDS, ARC
Zalcitabine	Hoffmann-La Roche	HIV infection, AIDS, ARC, with AZT
Zidovudine; AZT	Glaxo Wellcome	HIV infection, AIDS, ARC, Kaposi's sarcoma, in combination with other therapies

IMMUNO-MODULATORS

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
AS-101	Wyeth-Ayerst	AIDS

Bropirimine	Pharmacia Upjohn	advanced AIDS
Acemannan	Carrington Labs, Inc. (Irving, TX)	AIDS, ARC
CL246,738	American Cyanamid Lederle Labs	AIDS, Kaposi's sarcoma
EL10	Elan Corp, PLC (Gainesville, GA)	HIV infection
FP-21399	Fuki ImmunoPharm	blocks HIV fusion with CD4+ cells
Gamma Interferon	Genentech	ARC, in combination w/TNF (tumor necrosis factor)
Granulocyte Macrophage Colony Stimulating Factor	Genetics Institute Sandoz	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Hoeschst-Roussel Immunex	AIDS
Granulocyte Macrophage Colony Stimulating Factor	Schering-Plough	AIDS, combination w/AZT
HIV Core Particle Immunostimulant	Rorer	seropositive HIV
IL-2	Cetus	AIDS, in combination w/AZT
Interleukin-2	Hoffman-La Roche	AIDS, ARC, HIV, in combination w/AZT
IL-2	Immunex	AIDS, increase in CD4 cell counts
IL-2	Chiron	
Interleukin-2 (aldeslukin)		

Immune Globulin Intravenous (human)	Cutter Biological (Berkeley, CA)	pediatric AIDS, in combination w/AZT
IMREG-1	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
IMREG-2	Imreg (New Orleans, LA)	AIDS, Kaposi's sarcoma, ARC, PGL
Imuthiol Diethyl Dithio Carbamate	Merieux Institute	AIDS, ARC
Alpha-2 Interferon	Schering Plough	Kaposi's sarcoma w/AZT, AIDS
Methionine- Enkephalin	TNI Pharmaceutical (Chicago, IL)	AIDS, ARC
MTP-PE	Ciba-Geigy Corp.	Kaposi's sarcoma
Muramyl-Tripeptide Granulocyte Colony Stimulating Factor	Amgen	AIDS, in combination w/AZT
Remune	Immune Response Corp.	immunotherapeutic
rCD4 Recombinant Soluble Human CD4	Genentech	AIDS, ARC
rCD4-IgG hybrids		AIDS, ARC
Recombinant Soluble Human CD4	Biogen	AIDS, ARC
Interferon Alfa 2a	Hoffman-La Roche	Kaposi's sarcoma AIDS, ARC, in combination w/AZT
SK&F106528 Soluble T4	Smith Kline	HIV infection

Thymopentin	Immunobiology Research Institute (Annandale, NJ)	HIV infection
Tumor Necrosis Factor; TNF	Genentech	ARC, in combination w/gamma Interferon

ANTI-INFECTIVES

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Clindamycin with Primaquine	Pharmacia Upjohn	PCP
Fluconazole	Pfizer	cryptococcal meningitis, candidiasis
Pastille	Squibb Corp.	prevention of
Nystatin Pastille		oral candidiasis
Ornidyl	Merrell Dow	PCP
Eflornithine		
Pentamidine	LyphoMed	PCP treatment
Isethionate (IM & IV)	(Rosemont, IL)	
Trimethoprim		antibacterial
Trimethoprim/sulfa		antibacterial
Piritrexim	Burroughs Wellcome	PCP treatment
Pentamidine	Fisons Corporation	PCP prophylaxis
isethionate for inhalation		
Spiramycin	Rhone-Poulenc	cryptosporidial diarrhea
Intraconazole-	Janssen Pharm.	histoplasmosis;
R51211		cryptococcal meningitis
Trimetrexate	Warner-Lambert	PCP

OTHER

<u>Drug Name</u>	<u>Manufacturer</u>	<u>Indication</u>
Daunorubicin	NeXstar, Sequus	Kaposi's sarcoma
Recombinant Human Erythropoietin	Ortho Pharm. Corp.	severe anemia assoc. with AZT therapy
Recombinant Human Growth Hormone	Serono	AIDS-related wasting, cachexia
Megestrol Acetate	Bristol-Myers Squibb	treatment of anorexia assoc. w/AIDS
Testosterone	Alza, Smith Kline	AIDS-related wasting
Total Enteral Nutrition	Norwich Eaton Pharmaceuticals	diarrhea and malabsorption related to AIDS

5 It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical composition useful for the treatment of AIDS.

10 Preferred combinations are simultaneous or alternating treatments of with a compound of the present invention and an inhibitor of HIV protease and/or a non-nucleoside inhibitor of HIV reverse transcriptase. An optional fourth component in the combination is a nucleoside inhibitor of HIV reverse transcriptase, such as AZT, 3TC, ddC or ddI. A preferred inhibitor of HIV protease is indinavir, which is
15 the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999. Indinavir is generally administered at a dosage of 800 mg three times a day. Other preferred protease inhibitors are nelfinavir
20 and ritonavir. Another preferred inhibitor of HIV protease is saquinavir which is administered in a dosage of 600 or 1200 mg tid. Preferred non-

nucleoside inhibitors of HIV reverse transcriptase include efavirenz. The preparation of ddC, ddI and AZT are also described in EPO 0,484,071. These combinations may have unexpected effects on limiting the spread and degree of infection of HIV. Preferred combinations
5 include those with the following (1) indinavir with efavirenz, and, optionally, AZT and/or 3TC and/or ddI and/or ddC; (2) indinavir, and any of AZT and/or ddI and/or ddC and/or 3TC, in particular, indinavir and AZT and 3TC; (3) stavudine and 3TC and/or zidovudine; (4) zidovudine and lamivudine and 141W94 and 1592U89; (5) zidovudine and
10 lamivudine.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other
15 agent(s).

It will be understood that the scope of combinations of the compounds of this invention with AIDS antivirals, immunomodulators, anti-infectives or vaccines is not limited to the list in the above Table, but includes in principle any combination with any pharmaceutical
20 composition useful for the treatment of AIDS.

Indinavir is an inhibitor of HIV protease and is the sulfate salt of N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridyl-methyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentaneamide ethanolate, and is synthesized according to U.S. 5,413,999.
25 Indinavir is generally administered at a dosage of 800 mg three times a day.

The following examples are provided to further illustrate details for the preparation and use of the compounds of the present invention. The examples are not intended to be limitations on the
30 scope of the instant invention in any way, and they should not be so construed. Furthermore, the compounds described in the following examples are not to be construed as forming the only genus that is considered as the invention, and any combination of the compounds or their moieties may itself form a genus. Those skilled in the art
35 will readily understand that known variations of the conditions and

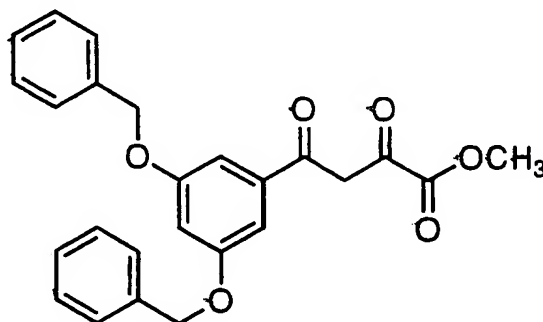
processes of the following preparative procedures can be used to prepare these compounds. All temperatures are in degrees Celsius unless noted otherwise.

Abbreviations: Ac represents acetyl; ACN is
 5 acetonitrile; Bn represents benzyl; Bu represents butyl; Calc'd represents calculated; DEAD is diethylazido-carboxylate; DME is dimethoxyethane; DMF is dimethyl formamide; DMSO is dimethylsulfoxide; EI represents electron impact; ES represents electrospray; Et represents ethyl; FAB represents fast atom
 10 bombardment; IPA is isopropyl alcohol; LDA is lithium diisopropylamide; L-Selectride® is lithium tri-sec-butylborohydride; MEK is methyl ethyl ketone; Me represents methyl; NMP is 1-methyl-2-pyrrolidinone; PDA is photodiode array; rt and RT represent room temperature; THF is
 15 tetrahydrofuran; TLC is thin layer (SiO₂) chromatography.

EXAMPLE 1

4-(3,5-Bis-benzyloxy-phenyl)-2,4-dioxobutanoic acid AI-2-1

20 Step 1: 4-(3,5-Bis-benzyloxy-phenyl)-2,4-dioxobutanoic acid methyl ester AI-1-1

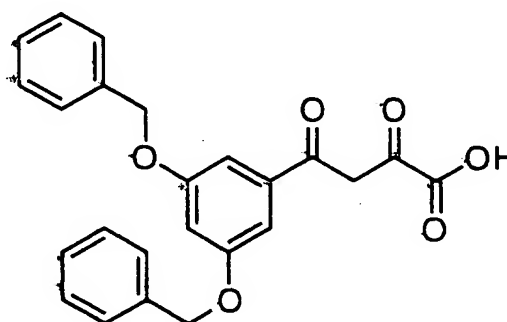


AI-1-1

A solution of 1-(3,5-bis-benzyloxy-phenyl)ethanone (3g, 9.0 mmole) in DME (20 mL) was treated with sodium hydride (0.54g, 60% dispersion in
 25 oil, 13.5 mmole) followed by dimethyl oxalate (1.3, 9.0 mmole) and a drop of methanol and the solution was warmed to 110°C. After 0.5 hours the reaction became dark brown and homogeneous. The reaction mixture

was poured into into 1N HCl and extracted with EtOAc three times, the combined organic layers were dried over MgSO₄, filtered and evaporated to give a yellow solid. The residue was dissolved in THF and absorbed to silica gel and added to the top of a pad of silica gel. The pad was eluted
 5 with CH₂Cl₂, which removed non-polar impurities, then with 20% MeOH/CH₂Cl₂, which eluted the product. The product was further purified by crystallization from EtOAc/Hexanes/Et₂O to give AI-1-1 as a orange foam. R_f=0.3 (97:3:1 CH₂Cl₃ / MeOH / HOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.4 (m, 10H), 7.24 (m, 2H), 7.01 (s, 1H), 6.84 (m, 1H), 5.1 (s,
 10 4H), 3.94, (s, 3H).

Step 2: 4-(3,5-Bis-benzoyloxy-phenyl)-2,4-dioxobutanoic acid AI-2-1



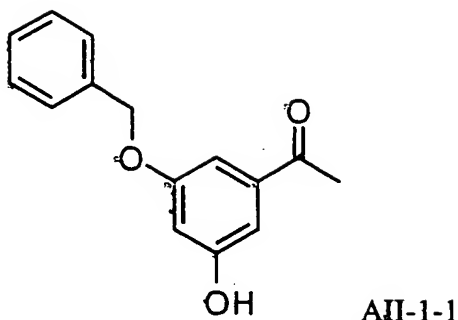
AI-2-1

A solution of AI-1-1 (1.5g, 3.47 mmole) was dissolved in 1:1 THF / MeOH
 15 (20 mL) and treated with 1 N NaOH (10 mL, 10 m mole) and stirred for one hour. The reaction mixture was washed with dilute ether, then acidified to pH2 with 1N HCl and extracted three times with EtOAc. The organic layers were combined, washed with 1 N HCl, dried over MgSO₄, filtered through a pad of CELITE diatomaceous earth and evaporated to
 20 dryness. The residue was triturated with ether to give AI-2-1 as bright yellow powder. ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.31 (m, 10H), 7.22 (s, 1H), 7.21 (s, 1H), 7.10 (s, 1H), 6.86 (m, 1H). mass spec (FAB, m+1) 405.13

EXAMPLE 2

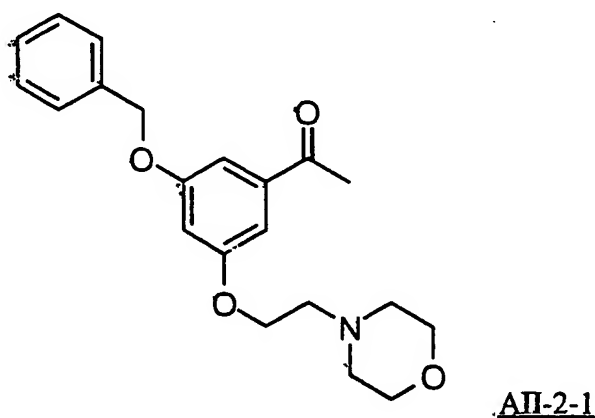
25 4-[3-Benzyloxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]-2,4-dioxobutanoic acid AII-3-1

Step 1: 1-(3-Benzyloxy-5-hydroxyphenyl)ethanone AII-1-1



A solution of 1-(3,5-bis-benzyloxyphenyl)ethanone (10g, 3.0 mmole) in 1:1 EtOH/Et₂O (200 mL) was treated with 10% palladium on carbon (3.4g) and hydrogen gas at balloon pressure for one hour with vigorous stirring. The solvent was evaporated and the residue chromatographed on silica gel eluting with 20% acetone / hexanes to give AII-1-1 as a white solid. R_f=0.27 (30% acetone / hexanes). ¹H NMR (400 MHz, CDCl₃) δ 7.4 (m, 5H), 7.16 (s, 1H), 7.05 (s, 1H), 6.7 (m, 1H), 5.82 (s, 1H), 5.08 (s, 2H), 2.55 (s, 3H).

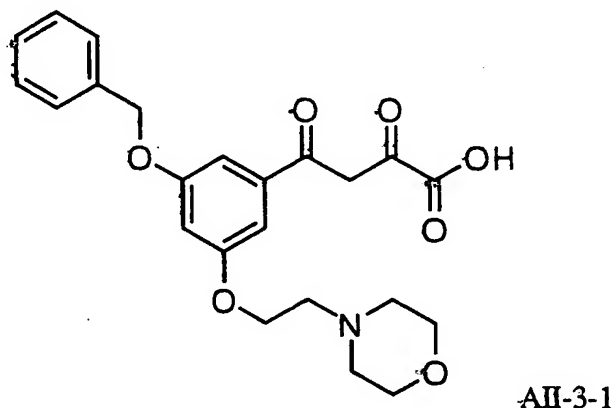
Step 2: 4-[2-(3-Acetyl-5-benzyloxy-phenoxy)-ethyl]morpholin-4-ium
AII-2-1



The free base of 4-(2-chloroethyl)morpholine hydrochloride (1.85g, 10 mmole) was formed and then combined with AII-1-1 (0.8g, 3.3 mmole), cesium carbonate (3.25g, 10 mmole) and dioxane (40 mL) and heated to 80°C for 4.5 hours. The solution was filtered, washed with EtOAc and concentrated. Column chromatography with 10-30% acetone / hexanes gave AII-2-1 as a brown syrup. R_f=0.39 (30% acetone / hexanes). ¹H

NMR (400 MHz, CDCl₃) δ 7.4 (m, 5H), 7.2 (s, 1H), 7.18 (s, 1H), 6.74 (m, 1H), 5.1 (s, 2H), 4.13 (t, J=5.6 Hz, 2H), 3.74 (t, J=4.5 Hz, 4H), 2.8 (t, J=5.6 Hz, 2H), 2.58 (m, 4H), 2.55 (s, 3H).

- 5 Step 3: 4-[3-Benzoyloxy-5-(2-morpholin-4-yl-ethoxy)phenyl]-2,4-dioxobutanoic acid AII-3-1



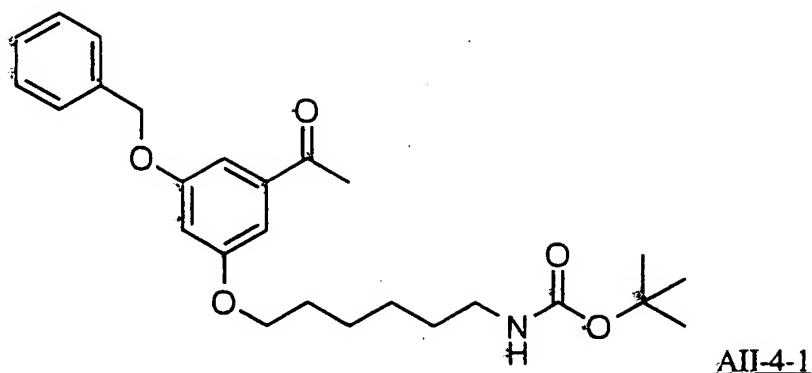
- 10 In a manner similar to that described for AI-1-1, AII-2-1 was treated with NaH and dimethyloxate in DME to give a mixture of AII-3-1 and its methyl ester. The mixture was treated with NaOH as described for AI-2-1 to give AII-3-1 as a yellow solid. ¹H NMR (400 MHz, D₂O) δ 7.4 (m, 5H), 6.97 (s, 1H), 6.86 (s, 1H), 6.56 (s, 1H), 5.05 (s, 2H), 4.05 (m, 2H), 3.6 (m, 5H), 2.7 (s, 2H), 2.5 (s, 4H). mass spec (m+1)=428

15

EXAMPLE 3

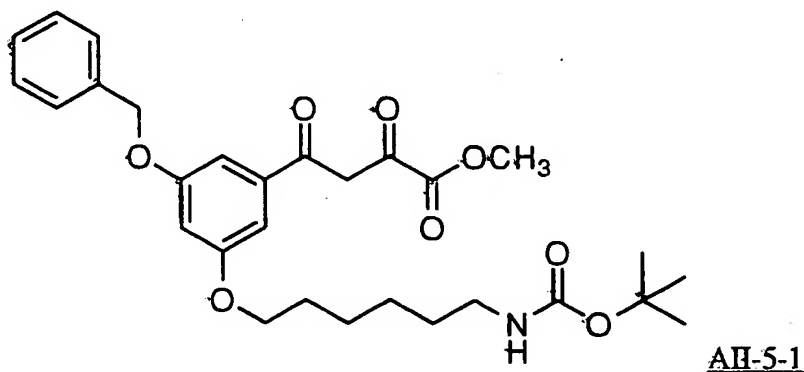
4-[3-Benzoyloxy-5-(6-*tert*-butoxycarbonylamino-hexyloxy)-phenyl]-2,4-dioxobutanoic acid AII-6-1

Step 1: [6-(3-Acetyl-5-benzoyloxy-phenoxy)-hexyl]carbamic acid-*tert*-butyl ester AII-4-1



In a manner similar to that described for AII-2-1, AII-1-1 was treated with (6-bromo-hexyl)-carbamic acid-*tert*-butyl ester (J. Med. Chem. 1994, 37, 2537-2551) to give AII-4-1. Rf=0.41 (80% acetone / hexanes); ¹H NMR (400 MHz, CDCl₃) δ 7.4 (m, 5H), 7.15 (s, 1H), 7.10 (s, 1H), 6.72 (m, 1H), 5.1 (s, 2H), 3.98 (t, J=6.4 Hz, 2H), 3.12 (m, 2H), 2.56 (s, 3H), 1.8 (m, 2H), 1.5 (m, 6H), 1.45 (s, 9H), 1.40 (m, 2H).

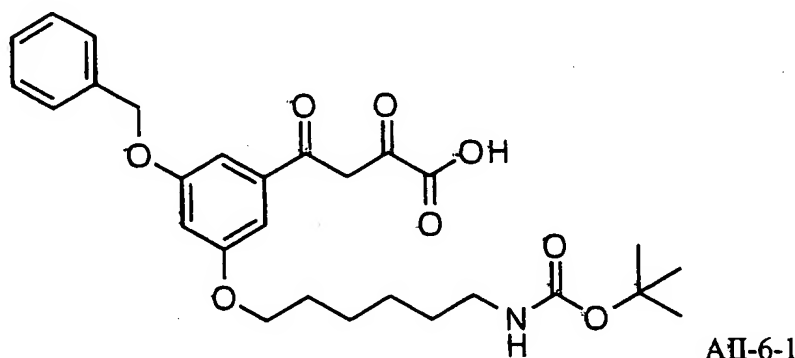
10 Step 2: 4-[3-Benzyloxy-5-(6-*tert*-butoxycarbonylamino-hexyloxy)phenyl]-2,4-dioxobutanoic acid methyl ester AII-5-1



15 Freshly prepared sodium methoxide (from 0.25g sodium metal in MeOH) was suspended in toluene (5 mL) and a solution of AII-4-1 (0.8g, 1.8 mmole) and dimethyloxalate (0.21g, 1.8 mmole) in toluene (5 mL) was added. The mixture was stirred for 2 hours, then quenched with 3 N HCl and extracted with EtOAc. The organic layer was dried with Na₂SO₄, filtered and evaporated. The residue was passed through a plug of silica gel as described for AI-1-1 and the resulting oil crystallized from ether to give AII-5-1 as a red solid. ¹H NMR (400 MHz, CDCl₃) δ 7.4

(m, 5H), 7.2 (s, 1H), 7.12 (s, 1H), 7.02 (s, 1H), 6.75 (m, 1H), 5.10 (s, 2H), 4.5 (bs, 1H), 4.0 (t, J=6.4 Hz, 2H), 3.95 (s, 3H), 3.13 (m, 2H), 1.8 (m, 2H), 1.5 (m, 6H), 1.45 (s, 9H), 1.4 (m, 2H).

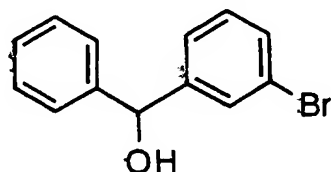
- 5 Step 3: 4-[3-Benzoyloxy-5-(6-*tert*-butoxycarbonylaminohexyloxy)phenyl]-2,4-dioxo-butanoic acid AII-6-1



- 10 In a manner similar to that described for AI-2-1, AII-5-1 was treated with NaOH to give AII-6-1 as a foamy yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 7.4 (m, 5H), 7.18 (s, 1H), 7.12 (s, 1H), 7.08 (s, 1H), 6.72 (s, 1H), 5.08 (s, 2H), 4.5 (bs, 1H), 4.0 (m, 2H), 3.13 (m, 2H), 1.8 (m, 2H), 1.6-1.3 (m, 17H).

EXAMPLE 4

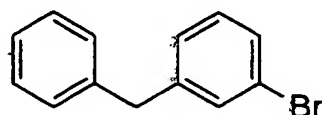
- 15 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid A-III-5-1
Step 1: (3-Bromophenyl)phenylmethanol AIII-1-1



- 20 To an oven dried 500 ml 3-neck flask fitted with temperature probe, magnetic stir bar, and argon inlet was added a solution of 2.5M *n*-butyl lithium in hexanes (20.8 ml, 0.052 mole) chilled to -78°C then diluted with diethyl ether (90 ml). To this was added dropwise by syringe over 30 minutes 1,3-dibromobenzene (11.80 g, 6.043 ml, 0.05 mole; activated basic

alumina pretreatment) keeping the internal temperature between -74°C and -78°C. The reaction was aged at -78°C for 2.5h before adding neat benzaldehyde (5.52 g, 5.29 ml, 0.052 mole) over 15 minutes then allowing the reaction mixture to slowly warm to room temperature as the bath discharged overnight. The reaction was quenched with 20 mL H₂O then acidified with 5.4 ml conc. HCl and extracted with EtOAc three times. The combined organic layers were washed with NaHCO₃, brine and dried over NaSO₄, filtered and evaporated in vacuo to give a clear yellow oil AIII-1-1 which crystallized to afford a white solid after washing with pet ether. R_f=0.14 (10% EtOAc/Hexanes). ¹H NMR (300 MHz, CDCl₃) δ 7.56 (s, 1H), 7.36-7.40 (m, 3H), 7.32-7.35 (m, 2H), 7.25-7.31 (m, 2H), 7.19 (m, 1H), 5.79 (s, 1H), 2.25 (s, 1H).

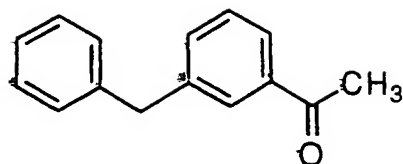
15 Step 2: (3-Benzyl)phenyl bromide AIII-2-1



AIII-2-1

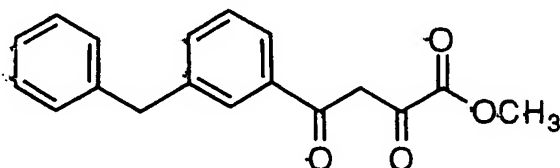
A solution of AIII-1-1 (4.10 g, 0.0156 mole) and triethylsilane (2.72 g, 3.71 ml, 0.0234 mole) in methylene chloride (40 ml) was chilled to 0°C under argon with stirring followed by addition of neat boron trifluoride etherate (3.32 g, 2.96 ml, 23.4 mmol). The reaction stirred at room temperature overnight. The reaction mixture was poured into 160 ml saturated NaHCO₃ and extracted with EtOAc three times, the combined organic layers were washed with brine and dried over Na₂SO₄, filtered and evaporated to afford colorless oil. Chromatographic purification using 5% EtOAc/hexanes afforded pure AIII-2-1; R_F=0.44 (5% EtOAc/Hexanes) ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.33 (m, 4H), 7.09-7.23 (m, 5H), 3.93 (s, 2H).

Step 3: 1-(3-Benzylphenyl)ethanone AIII-3-1

AIII-3-1

To an oven-dried 100 ml 3-neck flask fitted with temperature probe, magnetic stir bar, and argon inlet was added 1.10 g AIII-2-1 in 26 ml THF and cooled to -78°C. Following dropwise addition of 1.6 M *n*-butyl lithium in hexanes (4.90 ml, 49 mmole) over 15 minutes, the reaction was stirred for 1h at -78°C before adding neat *N*-methoxy-*N*-methylacetamide (551 mg, 53.4 mmole) over 20 minutes. The reaction mixture warmed slowly to room temperature as the bath discharged overnight. The reaction was quenched with 60 ml 10% KHSO₄ and extracted with Et₂O three times. The combined organic layers were washed with NaHCO₃, brine and dried over Na₂SO₄, filtered and evaporated *in vacuo* to give a clear yellow oil. Chromatographic purification using EtOAc/hexanes afforded pure AIII-3-1. R_f=0.10 (5% EtOAc/hexanes); 0.40 (30 acetone, 70 hexane, 1.5 HOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.80 (m, 2H), 7.39 (m, 2H), 7.29 (m, 2H), 7.19 (m, 3H), 4.05 (s, 2H), 2.6 (s, 3H).

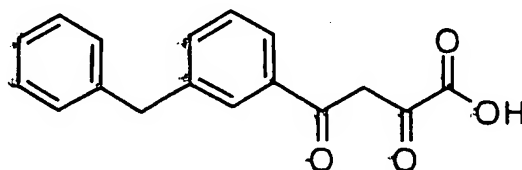
Step 4: 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid methyl ester
AIII-4-1

AIII-4-1

To an oven dried 100 ml flask fitted with magnetic stir bar, and argon inlet was added freshly prepared NaOMe (485 mg, 9.2 mmole) in 10 ml toluene and cooled to 0°C. Dimethyl oxalate (951 mg, 8.1 mmole) and AIII-3-1 (770 mg) were dissolved in dry dimethoxyethane (10 ml) and added by syringe at 0°C over 5 minutes. The flask was removed from ice bath and heated to 60°C overnight. The reaction was quenched with 60 ml saturated NH₄Cl and extracted with EtOAc three times. The

combined organic layers were washed with H₂O, brine and dried over Na₂SO₄, filtered and evaporated in vacuo to give an orange oil AIII-4-1. R_f=0.26 (30 acetone, 70 hexane + 1.5 HOAc); ¹H NMR (400 MHz, CDCl₃) δ 7.83 (m, 2H), 7.40 (m, 2H), 7.30 (m, 2H), 7.24 (m, 1H), 7.18 (m, 2H), 7.16 (s, 1H), 4.04 (s, 2H) 3.90 (m, 3H).

Step 5: 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid AIII-5-1



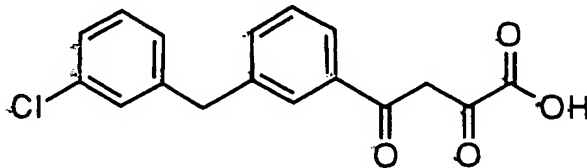
AIII-5-1

A solution of AIII-4-1 (900 mg, 2.9 mmole) was dissolved in 1:1 THF / MeOH (20 ml) and treated with 1 N NaOH (14.6 mL, 0.0146 mole) and stirred 1h. The reaction mixture was extracted with diethyl ether (2X), then acidified to pH 1-2 with 2N HCl (7.5 ml) and extracted three times with EtOAc. The organic layers were combined, washed with H₂O, brine and dried over Na₂SO₄, filtered and evaporated to afford a waxy solid. The residue was recrystallized from toluene-hexane to give a light yellow solid AIII-5-1. mp 118-119°C (uncorrected). R_f=0.12 (5 MeOH, 95 CH₂Cl₂, 5 HOAc). ¹H NMR (400 MHz, CDCl₃) δ 7.84 (m, 2H), 7.45 (m, 2H), 7.31 (m, 2H), 7.24 (m, 1H), 7.18 (m, 2H), 7.14 (s, 1H), 4.06 (s, 2H). mass spec (FAB, M+1) 283 m/e

20

EXAMPLE 5

In a manner similar to that described for AIII-5-1, the following compound was prepared:



AIII-5-2

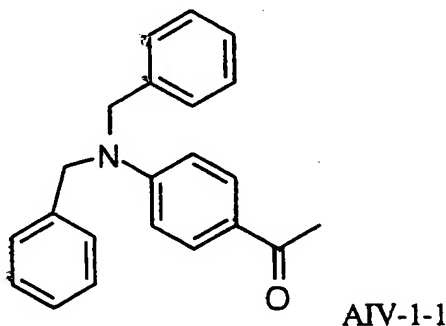
25 mp 102-103°C (uncorrected). R_f=0.18 (5 MeOH, 95 CH₂Cl₂, 5 HOAc)

^1H NMR (400 MHz, CDCl_3) δ 7.85 (m, 2H), 7.44 (m, 2H), 7.25 (m, 2H), 7.15 (m, 2H), 7.06 (m, 1H), 4.03 (s, 2H). mass spec (FAB, $\text{M}+1$) 317 m/e

EXAMPLE 6

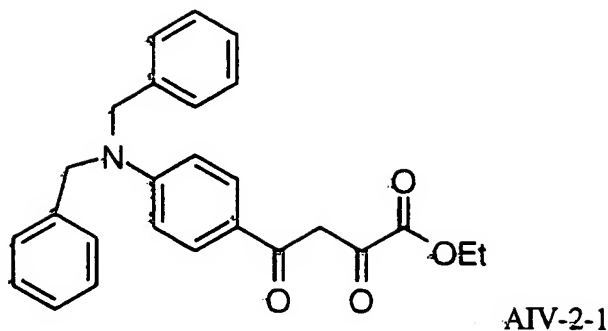
5 4-(4-Dibenzylaminophenyl)-2,4-dioxobutanoic acid AIV-3-1

Step 1: 1-(4-Dibenzylaminophenyl)ethanone AIV-1-1



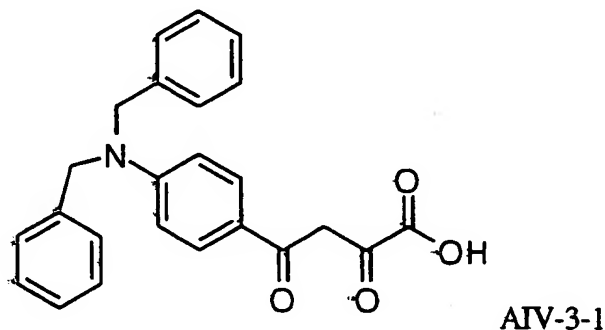
A mixture of 4-aminoacetophenone (.027 g, 2 mmol), benzyl bromide (1.71 g, .19 ml, 10 mmol), and cesium carbonate (1.63 g, 5 mmol) were
10 combined in 20 ml DMF and heated to 60 °C for 8 hr. The solvent was then removed and the residue partitioned between ethyl acetate/ H_2O and extracted. The combined organic extracts were washed with H_2O , brine, dried over Na_2SO_4 , filtered and the solvent removed. Purification by
radial disc chromatography (4:1 hexane/EtOAc) yielded 0.238 g (38%) of
15 AIV-1-1 as a clear oil. ^1H NMR (400 MHz, CDCl_3) δ 2.51 (s, 3H), 4.76 (s, 4H), 6.77 (d, 2H, $J = 8.97$ Hz), 7.26 (d, 4H, $J = 6.96$ Hz), 7.32 (t, 2H, $J = 7.14$ Hz), 7.37 (t, 4H, $J = 7.51$ Hz), 7.86 (d, 2H, $J = 9.16$ Hz).

20 Step 2: 4-(4-Dibenzylaminophenyl)-2,4-dioxobutanoic acid ethyl ester AIV-2-1



In a similar manner to example AI-1-1, 1-(4-dibenzylaminophenyl)-ethanone (0.238 g, 0.75 mmol) was reacted with diethyl oxalate (0.22 g, 0.2 ml, 1.5 mmol) and sodium ethoxide (0.1 g, 1.5 mmol) in 3 ml THF to
 5 yield 0.29 g (93%) of AIV-2-1 as a yellow solid. ¹H NMR (400 MHz, CDCl₃) δ 1.39 (t, 3H, J = 7.14 Hz), 4.36 (q, 2H, J = 7.14 Hz), 4.75 (s, 4H), 6.77 (d, 2H, J = 9.15 Hz), 6.95 (s, 1H), 7.21 (d, 4H, J = 6.96 Hz), 7.29 (t, 2H, J = 6.95 Hz), 7.35 (t, 4H, J = 7.69 Hz), 7.86 (d, 2H, J = 9.15 Hz).

10 Step 3: 4-(4-Dibenzylaminophenyl)-2,4-dioxobutanoic acid AIV-3-1

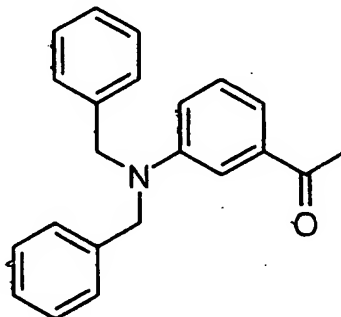


In a manner similar to example AI-2-1, 4-(4-dibenzylaminophenyl)-2,4-dioxobutanoic acid ethyl ester (0.29 g, 0.7 mmol) was hydrolyzed using 0.58 ml 1N LiOH in 5 ml THF to afford 0.237 g (87%) of AIV-3-1 as an
 15 orange solid. MP = 161 - 162 °C. ¹H NMR (400 MHz, CDCl₃) δ 4.76 (s, 4H), 6.79 (d, 2H, J = 9.34 Hz), 6.99 (s, 1H), 7.20 (d, 4H, J = 6.78 Hz), 7.30 (t, 2H, J = 7.14 Hz), 7.35 (t, 4H, J = 7.33 Hz), 7.86 (d, 2H, J = 9.15 Hz).

EXAMPLE 7

20 4-(3-Dibenzylaminophenyl)-2,4-dioxobutanoic acid AV-3-1

Step 1: 1-(3-Dibenzylaminophenyl)ethanone AV-1-1

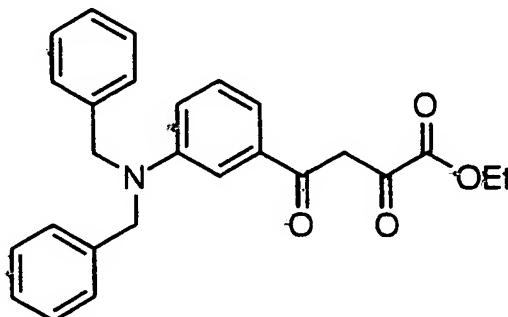


AV-1-1

In a similar manner to example AIV-1-1, 3-aminoacetophenone (0.27 g, 2 mmol) was reacted with benzyl bromide (1.71 g, 1.19 ml, 10 mmol) and cesium carbonate (1.63 g, 5 mmol) in 20 ml DMF at 60°C for 4 hr to give 0.346 g (55%) of AV-1-1 as a clear oil after purification by radial disc chromatography (4:1 hexane/CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 2.44 (s, 3H), 4.66 (s, 4H), 6.88 (ddd, 1H, J = 8.06, 2.75, 1.10 Hz), 7.18 - 7.26 (m, 7H), 7.26 - 7.33 (m, 3H), 7.37 (dd, 1H, J = 2.74, 1.47 Hz).

10

Step 2: 4-(3-Dibenzylaminophenyl)-2,4-dioxobutanoic acid ethyl ester AV-2-1



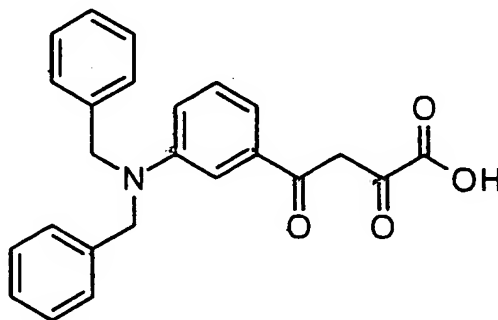
AV-2-1

In a manner similar to example AIV-1-1, 1-(3-dibenzylaminophenyl)-ethanone (0.346 g, 1.1 mmol) was reacted with diethyl oxalate (0.32 g, 0.3 ml, 2.2 mmol) and sodium ethoxide (0.15 g, 2.2 mmol) in 5 ml THF for 1 hr to give 0.48 g (100%) of AV-2-1 as a yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 1.37 (t, 3H, J = 7.14 Hz), 4.37 (q, 2H, J = 7.14 Hz), 4.71 (s, 4H),

15

6.93 (s, 1H), 6.95 (dd, 1H, $J = 2.75, 1.47$ Hz), 7.21 - 7.30 (m, 7H), 7.30 - 7.36 (m, 4H), 7.37 - 7.41 (m, 1H).

Step 3: 4-(3-Dibenzylaminophenyl)-2,4-dioxobutanoic acid AV-3-1



5

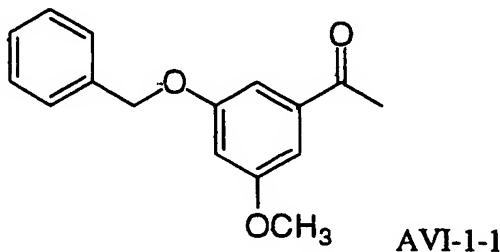
AV-3-1

In a similar manner to example AI-2-1, 4-(3-dibenzylaminophenyl)-2,4-dioxobutanoic acid ethyl ester (0.489 g, 1.1 mmol) was reacted with 3 ml 1N LiOH in 10 ml THF to yield 0.4 g (94%) of AV-3-1 as an orange resin. ^1H NMR (400 MHz, CDCl_3) δ 4.71 (s, 4H), 6.96 (dt, 1H, $J = 7.33, 2.20$ Hz).

10

EXAMPLE 8

1-(3-benzyloxy-5-methoxyphenyl)-2,4-dioxobutanoic acid AVI-3-1



AVI-1-1

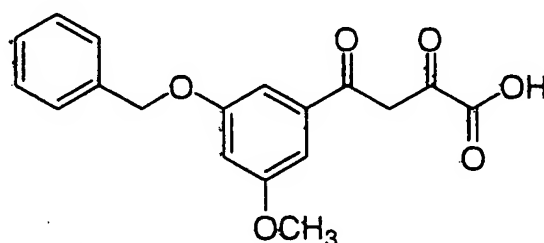
15 Step 1: 1-(3-Benzoyloxy-5-methoxyphenyl)-ethanone AVI-1-1

To a solution of 5-hydroxy-3-benzyloxyacetophenone (740 mg, 3.06 mmol) in DMF (10 mL) was added K_2CO_3 (845 mg, 6.12 mmol) followed by methyl iodide (0.38 mL, 6.10 mmol). After stirring at rt for 3 h, the reaction mixture was poured onto water (20 mL) and extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with water (20 mL), sat. NaCl (20 mL) and dried (MgSO_4). Concentration

20

followed by medium-pressure liquid chromatography on silica gel, eluting with 9:1/hexanes:EtOAc, afforded 0.550 g (70%) of product as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.33 (m, 5H), 7.18 (t, J = 1.6 Hz, 1H), 7.11 (t, J = 1.4 Hz, 1H), 6.74 (t, J = 2.2 Hz, 1H), 5.09 (s, 2H), 3.83 (s, 3H), 2.57 (s, 3H). mass spec (EI, M⁺) 256

Step 2: 1-(3-Benzyloxy-5-methoxyphenyl)-2,4-dioxobutanoic acid
 AVI-3-1



AVI-3-1

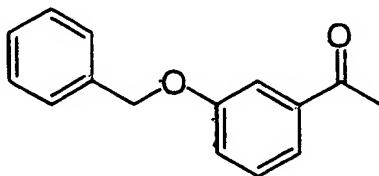
10 AI-1-1 was treated with NaOEt and diethyl oxalate to give the ethyl ester which was treated with aqueous HCl in dioxane to give AVI-3-1. mp 101-102 °C (uncorrected) ¹H NMR (400 MHz, d₆-DMSO) δ 7.48-7.44 (m, 2H), 7.39 (m, 2H), 7.34 (m, 1H), 7.25 (s, 1H), 7.14 (s, 1H), 7.06 (s, 1H), 6.89 (s, 1H), 5.19 (s, 2H), 3.81 (s, 3H). mass spec (FAB, M+H) 329

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EXAMPLE 9

1-(3-Benzyloxyphenyl)-2,4-dioxobutanoic acid AVI-3-2

Step 1: 1-(3-Benzyloxyphenyl)-ethanone AVI-1-2

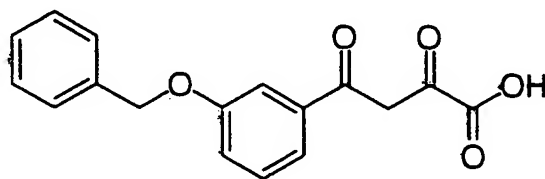


AVI-1-2

20 To a solution of benzyl alcohol (Aldrich, 1.08 g, 10.0 mmol) in benzene (40 mL) at rt was added 3-hydroxyacetophenone (Aldrich, 1.36 g, 10.0 mmol) followed by PPh₃ (2.62 g, 10.0 mmol). After cooling to 0 °C, DEAD (1.60 mL, 10.0 mmol) was added and the resulting mixture was stirred at rt. After 4 h, the reaction mixture was poured onto hexanes (50 mL) and

filtered through a pad of CELITE diatomaceous earth. The filtrate was concentrated and chromatographed on silica gel, eluting with 9:1/hexanes:EtOAc, to provide 2.01 g (89%) of product as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.60-7.54 (m, 2H), 7.47-7.32 (m, 6H), 7.21-7.17 (m, 1H), 5.12 (s, 2H), 2.59 (s, 3H). mass spec (EI, M⁺) 226

Step 2: 1-(3-Benzyloxyphenyl)-2,4-dioxobutanoic acid AVI-3-2



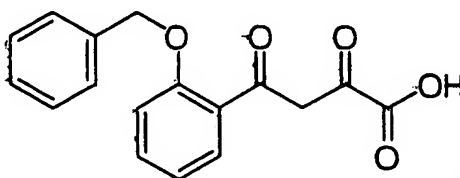
AVI-3-2

AVI-1-2 was treated with NaOEt and diethyl oxalate to give the ethyl ester which was treated with aqueous HCl in dioxane to give AVI-3-2. mp 109-114 °C (uncorrected) ¹H NMR (400 MHz, d₆-DMSO) δ 7.66 (dt, J = 1.4, 8.0 Hz, 1H), 7.63 (dd, J = 1.8, 2.3 Hz, 1H), 7.52-7.47 (m, 3H), 7.43-7.38 (m, 2H), 7.09 (s, 1H), 5.22 (s, 2H).

15

EXAMPLE 10

1-(2-Benzyloxyphenyl)-2,4-dioxobutanoic acid AVI-3-3



AVI-3-3

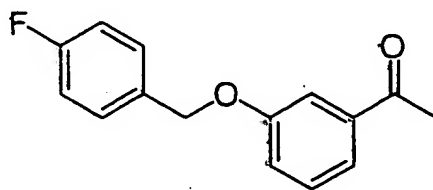
2-benzyloxyacetophenone (Chem Service) was treated with NaOEt and diethyl oxalate to give the ethyl ester which was treated with aqueous HCl in dioxane to give AVI-3-3. mp 136-138 °C (uncorrected). ¹H NMR (400 MHz, d₆-DMSO) δ 7.81 (dd, J = 1.8, 8.4 Hz, 1H), 7.62 (ddd, J = 1.8, 7.4, 8.4 Hz, 1H), 7.52 (m, 1H), 7.41-7.31 (m, 4H), 7.27 (s, 1H), 7.12 (t, J = 7.4 Hz, 1H), 5.23 (s, 2H). mass spec (FAB, M⁺H) 299

25

EXAMPLE 11

1-[3-(4-Fluorobenzyloxy)phenyl]-2,4-dioxobutanoic acid AVI-3-5

Step 1: 1-[3-(4-Fluorobenzoyloxy)phenyl]-ethanone AVI-1-5

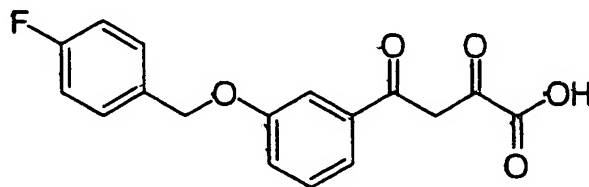


AVI-1-5

To a solution of 3-hydroxyacetophenone (Aldrich, 680 mg, 5.00 mmol) in DMF (10 mL) at rt was added K₂CO₃ (1.38-g, 10.0 mmol) and 4-

- 5 fluorobenzyl bromide (897 mg, 4.75 mmol). After 3 h, the reaction mixture was poured onto water (20 mL) and extracted with Et₂O (3 x 25 mL). The combined organic extracts were washed with 2.5 N NaOH (25 mL), sat. NaCl (25 mL) and dried (MgSO₄). Concentration followed by
10 medium-pressure liquid chromatography on silica gel, eluting with 9:1/hexanes:EtOAc, yielded 1.08 g (93%) of product as a clear oil. ¹H NMR (400 MHz, CDCl₃) δ 7.58-7.55 (m, 2H), 7.44-7.36 (m, 3H), 7.19-7.15 (m, 1H), 7.09 (m, 2H), 5.08 (s, 2H), 2.60 (s, 3H). mass spec (EI, M⁺) 244

Step 2: 1-[3-(4-Fluorobenzoyloxy)phenyl]-2,4-dioxobutanoic acid AVI-3-5



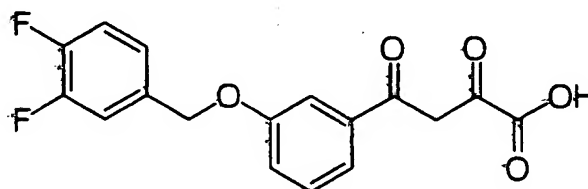
AVI-3-5

- AVI-1-5 was treated with NaOEt and diethyl oxalate to give the ethyl ester which was treated with aqueous HCl in dioxane to give AVI-3-5. mp 157-158 °C (uncorrected) ¹H NMR (400 MHz, d₆-DMSO) δ 7.66 (d, J =
20 7.7 Hz, 1H), 7.62 (t, J = 1.9 Hz, 1H), 7.56-7.47 (m, 4H), 7.33 (dd, J = 1.9, 7.7 Hz, 1H), 7.23 (m, 2H), 7.08 (s, 1H), 5.20 (s, 2H). mass spec (FAB, M+H) 317

EXAMPLE 12

- 25 1-[3-(3,4-Difluorobenzoyloxy)phenyl]-2,4-dioxobutanoic acid AVI-3-6

Step 1: 1-[3-(3,4-Difluorobenzoyloxy)phenyl]-2,4-dioxobutanoic acid
AVI-3-6



AVI-3-6

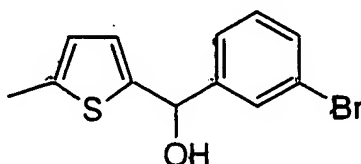
AVI-3-6 was prepared in a manner similar to that described for AVI-3-5
 5 by replacing 4-fluorobenzyl bromide with 3,4-difluorobenzyl bromide.
 mp 181-182 °C (uncorrected). ¹H NMR (400 MHz, d₆-DMSO) δ 7.68 (d, J =
 7.7 Hz, 1H), 7.63 (m, 1H), 7.60-7.55 (m, 1H), 7.53-7.43 (m, 2H), 7.36-7.33
 (m, 2H), 7.09 (s, 1H), 5.21 (s, 2H). mass spec (negative mode electro-
 spray, M-H) 333

10

EXAMPLE 13

4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-butyric acid E1

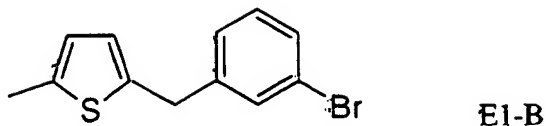
Step 1: (3-bromo-phenyl)-(5-methyl-thiophen-2-yl)-methanol E1-A

E1-A

15 To an oven dried 3-neck 250 mL round bottom flask equipped with argon
 inlet and digital thermometer was added 2.5M nBuLi in hexanes (15.24
 mL, 0.0381 mole) at -78°C. 1,3-Dibromobenzene (4.60 mL, 0.0381 mole)
 was then added dropwise via syringe to the solution, and this was
 allowed to stir for 2 hours. 5-methyl-2-thiophenecarboxaldehyde (5g,
 20 4.27mL, 0.0396 mole) was added over one hour. After an additional
 hour, 50 mL of water was poured into the reaction which was then
 acidified with conc. HCl. Extraction with EtOAc three times followed by
 drying over NaSO₄, filtration and removal of solvent gave E1-A as a
 brown oil that was taken on to the next step.

25

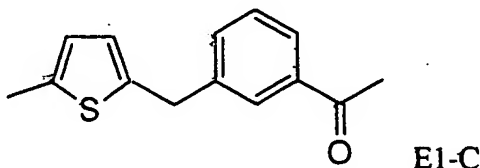
Step 2: 2-(3-bromobenzyl)-5-methylthiophene E1-B



A solution of crude E1-A (7.0 g, 0.0247 mole) and triethylsilane (5.9 mL, 0.0371 mole) in methylene chloride (30 mL) was chilled to 0° C under argon with stirring followed by addition of boron trifluoride etherate (4.67 mL, 0.0371 mole). The reaction was stirred at room temperature for two hours. The reaction mixture was poured into 150 mL of saturated sodium bicarbonate and extracted with methylene chloride 2 times. The combined organic layers were dried over sodium sulfate. Filtration and removal of solvent afforded a brown oil. Chromatographic purification using 100% hexanes afforded E1-B as a clear oil.

R_f=0.52 (100% Hexanes) ¹H NMR (400MHz, CDCl₃) δ 7.37-7.38 (m, 1H), 7.33-7.34 (m, 1H), 7.16 (s, 1H), 7.14-7.15 (m, 1H), 6.56 (m, 7.56), 4.02 (s, 2H), 2.41 (s, 3H).

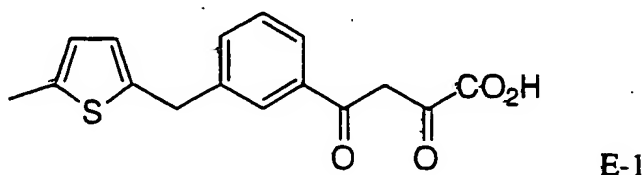
15 Step 3: 1-(3-(5-methylthiophen-2-ylmethyl)-phenyl)-ethanone E1-C



To an oven dried 3-neck flask fitted with temperature probe and argon inlet was added E1-B (4 g, 0.0150 mole) in 40 mL of THF. The reaction was cooled to -78°C and 2.5M nBuLi in hexanes (9.0mL 0.0225 mole) was added over one hour. The lithium salt of compound precipitated out of solution. Neat N-methoxy-N-methylacetamide (2.3g, 2.3mL 0.0225 mole) was added slowly which caused rxn to become homogenous. Once addition was complete the reaction was allowed to stir at room temperature for two hours. The reaction was poured into 20 mL of water and acidified with concentrated HCl. Extraction with EtOAc three times followed by drying over sodium sulfate, and subsequent removal of solvent gave a brown oil. Chromatographic purification using a 88:12 mixture of Hexanes/EtOAc afforded E1-C as a clear oil.

R_f=0.42 (10% EtOAc/Hexanes) ¹H NMR (400MHz, CDCl₃) δ 7.84 (s, 1H), 7.82, 7.80 (d, 1H), 7.37-7.45 (m, 2H), 6.58-6.55 (m, 2H), 4.12 (s, 2H), 2.58 (s, 3H), 2.41 (s, 3H).

5 Step 4: 4-[3-(5-methylthiophen-2-ylmethyl)-phenyl]-2,4-dioxo-butyric
acid E1



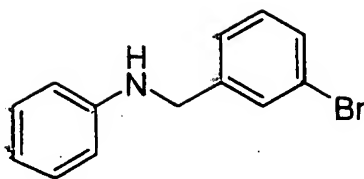
To a solution of E1-C (1g, 0.00446 mole) and diethyloxylate (0.67mL, 0.00491 mole) in THF (8mL) was added NaOEt (0.46g, 0.00669 mole) under an atmosphere of Argon. After two hours the reaction was poured into an aqueous solution of potassium hydrogen sulfate, extracted with EtOAc three times, dried over sodium sulfate, and the solvent removed to give the ethyl ester. Immediately following workup the ester was submitted to 3N NaOH (7.4 mL, 0.0223 mole) in a 5:2 mixture of THF/MeOH (20 mL). After one hour the reaction was poured into saturated sodium bicarbonate solution and extracted two times with ether. The aqueous layer was acidified with a solution of 10% KHSO₄ which caused a large amount of solids to crash out. The aqueous layer was extracted with EtOAc eight times, the organic layer was dried over NaSO₄, filtered and concentrated to give a solid which was crystallized from CH₂Cl₂ and pet. ether. Collected pure E1 as a yellow solid by filtration. ¹H NMR (400MHz, CDCl₃) δ 7.88-7.85 (m, 2H), 7.50-7.44 (m, 2H), 7.15 (s, 1H), 6.60-6.57 (m, 2H), 4.14 (s, 2H), 2.42, (s, 3H). Exact mass (M +NH₄) = 320.0951.

25

EXAMPLE 14

4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-butyric acid E2

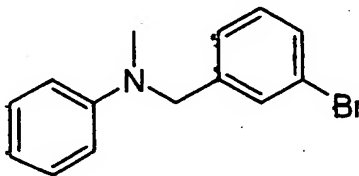
Step 1: (3-bromo-benzyl)-phenyl-amine E2-A

E2-A

To a solution of aniline (1.26g, 1.23 mL, 0.0135 mole) and 3-bromo-benzaldehyde (2.5g, 1.58 mL, 0.0135 mole) in MeOH (20mL) under argon
5 was added HOAc to adjust pH to 5.5. After 45 minutes sodium cyanoborohydride (1.11g, 0.0176 mole) was added and pH readjusted to 5.5. After 16 hours the reaction was poured into saturated aqueous sodium bicarbonate solution, extracted 3 times with EtOAc, dried over NaSO₄, filtered and concentrated. Chromatographic purification with
10 95:5 Hexanes/EtOAc afforded E2-A as an oil.
R_f=0.28 (5% EtOAc/Hexanes) ¹H NMR (400MHz, CDCl₃) δ 7.52 (s, 1H), 7.40-7.38 (d, 1H, j=7.33 Hz), 7.28, 7.30 (d, 1H, j=7.69 Hz), 7.21-7.14 (m, 3H), 6.75-6.71 (t, 1H, j=7.42 Hz), 6.62-6.59 (d, 2H, j=7.87 Hz) 4.31 (s, 2H), 4.06 (broad, 1H).

15

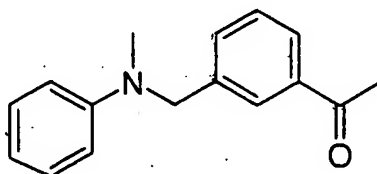
Step 2: (3-bromo-benzyl)-methyl-phenyl-amine E2-B

E2-B

To a solution of E2-A (1.5 g, 0.00572 mole) in DMF (25 mL) and under argon at 0°C was added NaH (0.15 g, 0.00629 mole) and this was stirred
20 for 15 minutes followed by addition of iodomethane (0.40 mL, 0.00629 mole) which was passed through basic alumina. Reaction required an additional 1 equivalent each of NaH and iodomethane. After 24 hours poured into 50 mL of saturated sodium bicarbonate solution, extracted with EtOAc 3 times, dried over sodium sulfate, filtered, and
25 concentrated. Chromatographic purification using 90:10 Hexanes/Ethyl acetate afforded E2-B.

Rf=0.45 (5% EtOAc/Hexanes) ^1H NMR (400MHz, CDCl_3) δ 7.40–7.36 (m, 2H), 7.26–7.15 (m, 4H), 6.76–6.72 (m, 3H), 4.49 (s, 2H), 3.02 (s, 3H).

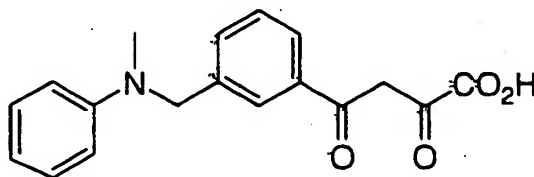
Step 3: 1-{3-[(methyl-phenyl-amino)-methyl]-phenyl}-ethanone E2-C



E2-C

Product from E2-B (1 g, 0.00361 mole), triethylamine (2mL, 0.0144 mole), thallium acetate (1.05g, 0.00937 mole), palladium acetate (0.2g, 0.000903 mole), butyl vinyl ether (1.81 mL, 0.0181 mole), and 1,3-Bis(diphenylphosphino)-propane (0.4g, 0.000975 mole) were combined in a pressure tube in anhydrous DMF (8 mL) under argon at 100°C overnight. Passed mixture through a pad of CELITE diatomaceous earth which was washed several times with EtOAc. Solvent was then removed and the residue dissolved in THF to which 1N HCl was added (14 mL, 0.0144 mole). After one hour poured into 20 mL of saturated sodium bicarbonate solution and extracted with EtOAc dried over NaSO_4 , filtered and concentrated. Chromatographic purification with 80:20 Hexanes/EtOAc afforded purified E2-C.
 Rf= 0.29 (10% EtOAc/Hexanes) ^1H NMR (400MHz, CDCl_3) δ 7.91–7.87 (m, 2H), 7.48–7.44 (m, 2H), 7.3–7.25 (m, 2H), 6.82–6.76 (m, 3H), 4.61 (s, 2H), 3.07 (s, 3H), 2.61 (s, 3H).

Step 4: 4-{3-[(methyl-phenyl-amino)-methyl]-phenyl}-2,4-dioxobutyric acid E2



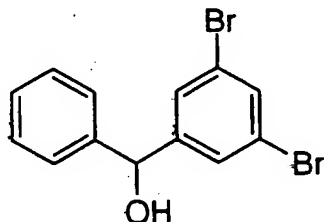
E2

To a solution of E2-C (0.4 g, 0.00167 mole) and dimethyloxylate (0.22g 0.00184 mole) in THF (5mL) was added NaOMe (0.4g, 0.00334 mole) under an atmosphere of Argon. After two hours the reaction was poured into an aqueous solution of potassium hydrogen sulfate, extracted with EtOAc three times, dried over sodium sulfate, and the solvent removed to give the methyl ester. Immediately following workup the ester was submitted to 1N NaOH (7.0 mL, 0.00167 mole) in THF (20 mL). After 1 hour the reaction was poured into saturated sodium bicarbonate solution and extracted two times with ether. The aqueous was with 3N HCl, extracted with EtOAc three times, and the organic layers dried over NaSO₄, filtered and concentrated to give solid pure E2.
1H NMR (400MHz, CDCl₃) δ 7.91-7.81 (m, 2H), 7.48-7.44 (m, 2H), 7.28-7.22 (m, 2H), 7.16 (s, 1H), 6.81-6.77 (m, 3H), 4.59 (s, 2H), 3.09 (s, 3H).
Exact mass found (m+H) = 312.1230.

15

EXAMPLE 15

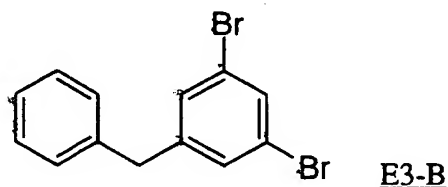
4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid E3

Step 1: (3,5-dibromo-phenyl)-phenyl-methanol E3-AE3-A

20 To a solution of 1,3,5-tribromobenzene (10 g, 0.0318 mole) in ether (500g), under argon was added nBuLi in hexanes (13.4 mL, 0.0318 mole) dropwise at -78°C. During the initial cooling of the tribromobenzene in ether some solids crashed out of solution. After addition of nBuLi was complete the reaction was allowed to stir for 0.5 hours at which time
25 neat benzaldehyde (3.55 mL, 0.035 mole) was added dropwise to the vigorously stirred reaction mixture. Once addition was complete the reaction was allowed to reach 0°C and 100 mL of HCl was added to the mixture. This was extracted with ether two times, dried with brine and over sodium sulfate and concentrated to give an oil. The crude product

was purified by chromatography with 5% EtOAc/Hexanes to afford E3-A as a colorless oil that solidified on the bench. $R_f = 0.44$ (5%EtOAc/Hexanes) $^1\text{H NMR}$ (400MHz, CDCl_3) δ 7.56–7.55 (m, 1H), 7.48–7.47 (m, 2H), 7.39–7.29 (m, 5H), 5.75 (d, 1H, $j=3.48$ Hz), 2.28–2.27 (d, 1H, $j=3.48$ Hz).

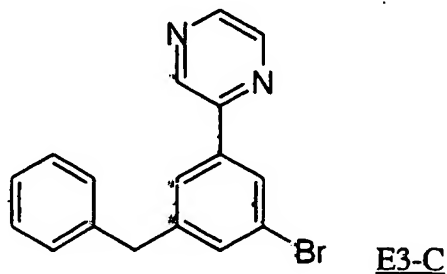
Step 2: 3-bromo-5-benzyl-bromobenzene E3-B



A solution of E3-A (2.0 g, 0.00548 mole) and triethylsilane (1.39 mL, 0.00877 mole) in methylene chloride (20 mL) was chilled to 0°C under argon with stirring followed by addition of boron trifluoride etherate (1.10 mL, 0.00877 mole). The reaction was stirred at room temperature overnight. The reaction mixture was poured into 75 mL of saturated sodium bicarbonate and extracted with methylene chloride two times.

The combined organic layers were dried over sodium sulfate, filtered and the solvent removed. Chromatographic purification using 1% EtOAc/Hexanes afforded E3-B. $R_f=0.72$ (5%EtOAc/hexanes) $^1\text{H NMR}$ (400MHz, CDCl_3) δ 7.50 (s, 1H), 7.37–7.21 (m, 5H), 7.16–7.14 (m, 2H), 3.91 (s, 2H).

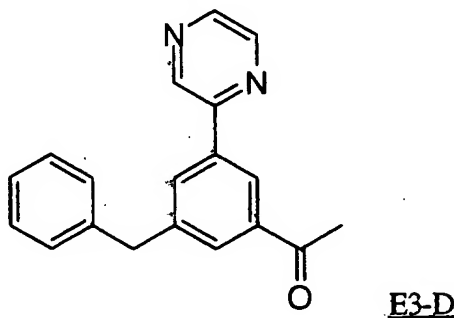
Step 3: 2-(3-benzyl-5-bromo-phenyl)-pyrazine E3-C



To a solution of E3-B (1 g, 0.00307 mole) in THF (20 mL) under argon at -78°C was added 2.4M nBuLi in hexanes (1.4 mL, 0.00337 mole)

dropwise. After 45 minutes of stirring, the solution was treated with 0.5m ZnCl₂ in THF (6.14 mL 0.00337 mole) and this was warmed to 0°C. To the reaction was added a cold mixture of chloropyrazine (0.35 mL, 0.00307 mole) and tetrakis(triphenylphosphine) palladium (18 mg, 0.0000154 mole) in THF (5 mL) and the reaction was heated to reflux for two hours. The reaction was then cooled, concentrated and treated with EtOAc and washed with 6% aqueous solution of diaminotetraacetic acid disodium salt dihydrate two times. The EtOAc layer was dried over sodium sulfate, filtered and concentrated. Chromatographic purification with 15% EtOAc/hexanes afforded a clear oil E3-C. R_f=0.17 (20%EtOAc/hexanes) ¹H NMR (400MHz, CDCl₃) δ 8.95 (s, 1H), 8.62-8.61 (m, 1H), 8.52 (m, 1H), 8.02 (s, 1H), 7.77 (s, 1H), 7.43 (s, 1H), 7.32-7.20 (m, 5H), 4.04 (s, 2H).

15 Step 4: 1-(3-benzyl-5-pyrazin-2-yl-phenyl)-ethanone E3-D

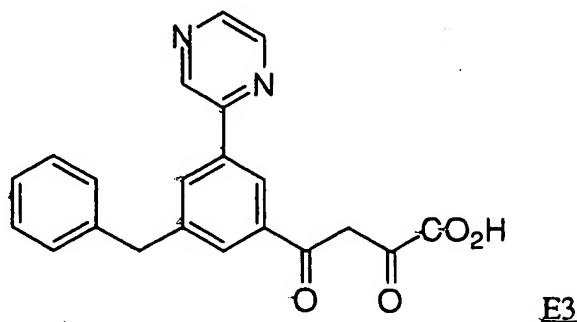


E3-C (0.29 g, 0.000926 mole), triethylamine (0.52mL, 0.00370 mole), thallium acetate (0.27 g, 0.00102 mole), palladium acetate (52 mg, 0.000232 mole), butyl vinyl ether (0.60 mL, 0.00463 mole), and 1,3-bis(diphenylphosphino)-propane (0.1g, 0.000242 mole) were combined in a pressure tube in anhydrous DMF (4 mL) under argon at 100°C overnight. The mixture was passed through a pad of CELITE diatomaceous earth which was washed several times with EtOAc. The solvent was then removed and the residue dissolved in THF to which 1N HCl was added (3.70 mL, 0.00370 mole). After one hour the reaction was poured into 15 mL of saturated sodium bicarbonate solution and extracted with EtOAc. The organic layers were dried over NaSO₄, filtered and

concentrated. Chromatographic purification with 70:30 Hexanes/EtOAc afforded purified E3-D as a clear oil. $R_f =$ ^1H NMR (400MHz, CDCl_3) δ 9.04 (s, 1H), 8.65-8.64 (m, 1H), 8.55-8.54 (m, 1H), 8.44 (s, 1H), 8.06 (s, 1H), 7.91 (s, 1H), 7.33-7.22 (m, 5H), 4.14 (s, 2H), 2.65 (s, 3H).

5

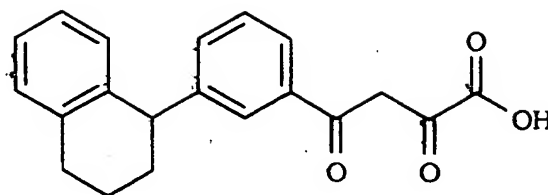
Step 5: 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid E3



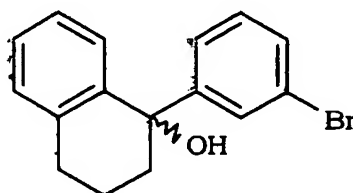
To a solution of E3-D (0.17 g, 0.000590 mole) and dimethyloxylate (76 mg 0.000650 mole) in THF (7mL) was added NaOMe (50 mg, 0.000884 mole) under an atmosphere of Argon. After one hour the reaction was poured into an aqueous solution of potassium hydrogen sulfate, extracted with EtOAc three times, dried over sodium sulfate, and the solvent removed to give the methyl ester. Immediately following workup the ester was submitted to 1N NaOH (1.48 mL, 0.00148 mole) in THF (10 mL). After 1 hour the reaction was poured into saturated sodium bicarbonate solution and extracted three times with ether. The aqueous layer was acidified with 3N HCl, extracted with EtOAc three times, the organic layers were dried over NaSO_4 , filtered and concentrated to give E3 as a pure white solid. ^1H NMR (400MHz, DMSO) δ 9.41 (m, 1H), 8.76-8.75 (m, 1H), 8.67 (m, 1H), 8.60 (s, 1H), 8.36 (s, 1H), 8.08 (s, 1H), 7.36-7.29 (m, 4H), 7.22-7.19 (m, 2H), 4.17 (s, 2H). Exact mass found ($m+H$) = 361.1196

EXAMPLE 16

2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyric acid
25 (isomers A and B) (G1 and G2)

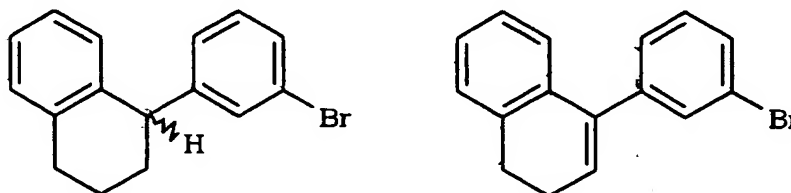


Step 1: Synthesis of 1-(3-bromophenyl)-1,2,3,4-tetrahydronaphthalen-1-ol



To a solution of 1 g (4.2 mmol) 1,3-dibromobenzene in 10 mL
 5 diethyl ether was added .096 g (4 mmol) magnesium metal turnings.
 This mixture was stirred until all of the magnesium was consumed, at
 which time .29 g (2 mmol) 1-tetralone was added dropwise in 2 mL
 diethyl ether. The reaction was then heated to reflux for 30 min, after
 which the cooled reaction was quenched with a 10% HCl solution and
 10 extracted three times with ethyl acetate. The combined organic layers
 were washed with water, brine, dried over anhydrous sodium sulphate,
 filtered, and the solvent removed *in vacuo* to afford the crude product
 which was used without further purification.

15 Step 2. Synthesis of 1-(3-bromophenyl)-1,2,3,4-tetrahydronaphthalene
 and 4-(3-bromophenyl)-1,2-dihydronaphthalene.



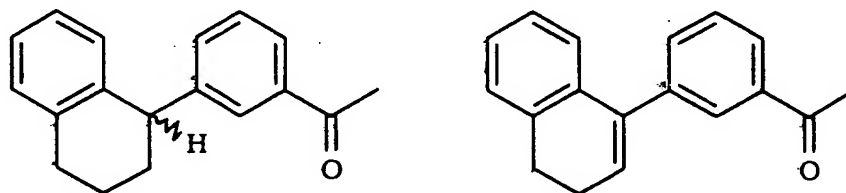
Into an ice cooled solution of .671 g (2.2 mmol) of 1-(3-bromophenyl)-
 1,2,3,4-tetrahydronaphthalen-1-ol and .386 g (3.3 mmol)
 20 triethylsilane in 5 mL methylene chloride was added .471 g (3.3 mmol)
 boron trifluoride diethyl etherate dropwise. After stirring the reaction

for 6 hr, the solution was slowly poured into 10 mL 10% sodium carbonate solution and extracted three times with methylene chloride. The combined organic layers were washed with water, brine, dried over anhydrous sodium sulphate, filtered, and the solvent removed *in vacuo*.

- 5 Purification by radial chromatography (5:1 hexane/ethyl acetate) followed by a second purification (7:1 hexane/methylene chloride) a 2.5:1 mixture of 1-(3-bromophenyl)-1,2,3,4-tetrahydronaphthalene and 4-(3-bromophenyl)-1,2-dihydronaphthalene which was used without further purification.

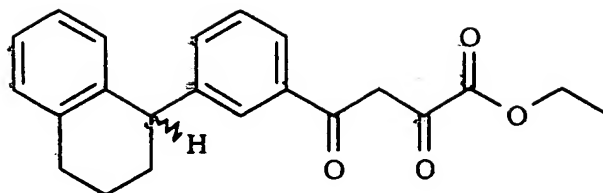
10

Step 3. Synthesis of 1-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]-
ethanone and 1-[3-(1,2-dihydronaphthalen-1-yl)-phenyl]-ethanone



- To a solution of .276 g of the above mixture dissolved in 10 mL of a 1:1
15 mixture of diethyl ether/tetrahydrofuran and cooled to -76°C was slowly added .42 mL of a 2.5M solution of *n*-butyllithium in hexanes so the temperature did not exceed -70 °C. After the addition, the reaction was stirred for an addition 30 min, after which time .118 mL *N*-methoxy-*N*-methyl acetamide was added. This mixture was allowed to stir for 15
20 min, then warmed to ambient temperature and stirred for 18 hr. The reaction was then quenched by the addition of 50 mL water and extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water, brine, dried over anhydrous sodium sulphate, filtered, and the solvent removed *in vacuo*. Subsequent purification by
25 preparative HPLC afforded three compounds: the olefin, enantiomer A and enantiomer B. The absolute stereochemistry of the enantiomers was not determined.

- Step 4: Synthesis of 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyric acid ethyl ester (isomers A and B)
30



Isomer A: Into 1 mL distilled tetrahydrofuran was placed .046 g (.18 mmol) of 1-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]-ethanone (isomer A), .054 g (.37 mmol) diethyl oxalate, and .025 g (.37 mmol) sodium ethoxide. After stirring for 1.5 hr, excess 10% citric acid solution was added and the THF removed *in vacuo*. The residue was partitioned between water and ethyl acetate and extracted. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate, filtered, and the solvent removed *in vacuo* to afford the title compound which was used without further purification.

Isomer B: As described above, .048 g (.19 mmol) of 1-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]-ethanone (isomer B), .056 g (.38 mmol) diethyl oxalate, and .026 g (.38 mmol) sodium ethoxide were reacted to give the title compound which was used without further purification.

Step 5: Synthesis of 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyric acid (isomers A and B)

Isomer A: 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyric acid ethyl ester (isomer A from above) was dissolved in 2 mLs methanol, and to it was added 1 mL of a 1M solution of sodium hydroxide in water. After stirring for 4hr, the reaction was poured into 5 mL sodium hydroxide and extracted three times with diethyl ether. The aqueous layer was then acidified via the addition of excess 10% citric acid and extracted three times with ethyl acetate. The ethyl acetate extracts were combined and washed with water, brine, dried over anhydrous sodium sulfate, filtered, and the solvent removed *in vacuo*. The residue was triturated in 3:1 hexane/diethyl ether, filtered and the solvent removed *in vacuo* to yield the title compound as a yellow solid.

¹H NMR (CDCl₃) δ 1.72 - 1.91(3H,m), 2.20(1H,m), 2.80 - 3.00(2H,m),

4.22(1H, t, J=7.14Hz), 6.77(1H, d, J=7.69Hz), 7.03(1H, t, J=7.42Hz), 7.11 - 7.19(3H,m), 7.31(1H, d, J=7.69Hz), 7.41(1H, t, J=7.69Hz), 7.80(1H,s), 7.84(1H, d, J=7.88Hz)

CHN Calc. (C₂₀H₁₈O₄ • 1EtOAc) 73.98, 5.72; Fnd. 73.68, 6.04

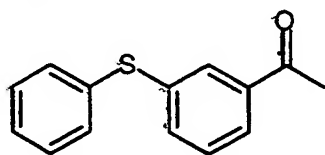
- 5 Isomer B: In a similar manner to the above, 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyric acid ethyl ester (isomer B from above) was reacted in 2 mL methanol with 1 mL 1M sodium hydroxide to afford the title compound as a yellow solid.
- 1H NMR (CDCl₃) δ 1.72 - 1.91(3H,m), 2.20(1H,m), 2.80 - 3.00(2H,m),
- 10 4.22(1H, t, J=7.14Hz), 6.77(1H, d, J=7.69Hz), 7.03(1H, t, J=7.42Hz), 7.11 - 7.19(3H,m), 7.31(1H, d, J=7.69Hz), 7.41(1H, t, J=7.69Hz), 7.80(1H,s), 7.84(1H, d, J=7.88Hz)
- CHN Calc. (C₂₀H₁₈O₄ • 1EtOAc) 73.98, 5.72; Fnd. 73.68, 5.90

15

EXAMPLE 17

2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid L1

Step 1: 1-(3-Phenylsulfanyl-phenyl)-ethanone L1-A

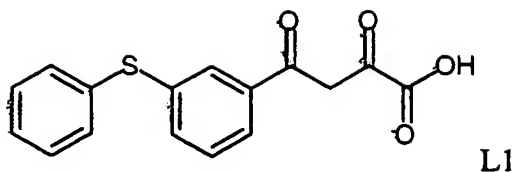


L1-A

- A mixture of potassium carbonate (1.20 g, 9.08 mmol), 0.17 M Ni(II)Br₂
- 20 (2.12 mL, 0.36 mmol), 1,1'-bis(diphenylphosphino)ferrocene (dppf, 403 mg, 0.73 mmol), zinc powder (119 mg, 1.82 mmol), and *N*-methyl-2-pyrrolidinone (NMP, 10 mL) was stirred at room temperature for one hour in dried glassware under argon. Thiophenol (932 µL, 9.08 mmol) and 3'-iodoacetophenone (1.88 mL, 13.6 mmol) were then introduced and
- 25 the mixture was stirred for three hours. The resulting mixture was directly chromatographed using 5 % EtOAc / hexane as the elutant. Pure fractions were combined and concentrated to afford L1-A as a yellow oil. R_f = 0.49 (10% EtOAc / hexane). 1H NMR (400 MHz, CDCl₃) δ 7.89 (m, 1H), 7.79 (m, 1H), 7.56 (m, 1H), 7.29-7.40 (m, 6H), 2.58 (s, 3H).

30

Step 2: 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid L1

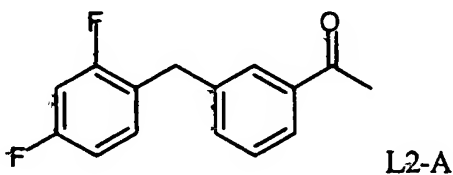


In a manner similar to example AIV-2-1, 2,4-dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid ethyl ester was formed and the crude material was hydrolyzed in a manner similar to example AIV-3-1 using 1N NaOH to afford L-1 as a yellow solid. $R_f = 0.32$ (6:6:94 MeOH / AcOH / CH₂Cl₂).
¹H NMR (400 MHz, CDCl₃) δ 7.91 (m, 1H), 7.81 (m, 1H), 7.48 (m, 1H), 7.43 (m, 1H), 7.33-7.43 (m, 5H), 7.09 (s, 1H).
 mass spec (FAB, M+1) 301 m/e.

10

EXAMPLE 18

4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid L2

Step 1: 1-[3-(2,4-Difluoro-benzyl)-phenyl]-ethanone L2-A

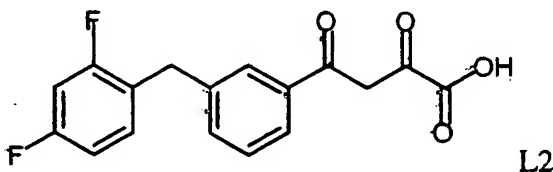
15 To an oven dried three-necked 100 mL round bottom flask fitted with argon inlet, temperature probe and stir bar was added zinc powder (793 mg, 12.2 mmol), 1,2-dibromoethane (21 μ L, 0.24 mmol), and THF (2 mL). The mixture was brought to reflux two times using a heat gun then cooled to 0°C at which time α -bromo-2,4-difluorotoluene (781 μ L, 6.10
 20 mL) in THF (3 mL) was added slowly keeping the temperature < 3°C. To another 3-necked round bottom flask fitted as above was added bis(dibenzylideneacetone)palladium (Pd(dba)₂, 234 mg, 0.41 mmol), tris(2-furyl)phosphine (tfp, 189 mg, 0.81 mmol), and THF (5 mL). The mixture was stirred 10 minutes at room temperature then cooled to 0°C
 25 at which time 3'-iodoacetophenone (562 μ L, 4.06 mmol) in THF (1 mL) was added. The flask was flushed with argon and the zinc mixture was pipetted in. After stirring 5 minutes at 0°C, the reaction was left to stir

over night at room temperature. The next morning the reaction was quenched with sat. NH_4Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated to a brown oil. The crude

- 5 product was chromatographed on silica gel using 5% EtOAc / hexane as elutant. Pure product fractions were combined and concentrated to afford L2-A as a yellow oil. $R_f = 0.22$ (5% EtOAc / hexane). ^1H NMR (400 MHz, CDCl_3) δ 7.81 (m, 2H), 7.39 (m, 2H), 7.11 (m, 1H), 6.81 (m, 2H), 4.02 (s, 2H), 2.56 (s, 3H).

10

Step 2: 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid L2



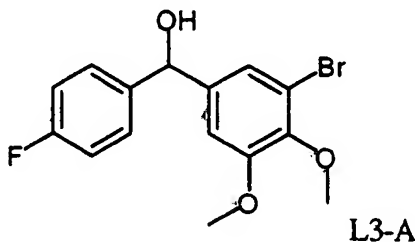
- 15 In a manner similar to example AIV-2-1, 4-[3-(2,4-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid ethyl ester was formed and the crude material was hydrolyzed in a manner similar to example AIV-3-1 using 1N NaOH to afford L2 as a yellow solid. $R_f = 0.60$ (6:6:94 MeOH / AcOH / CH_2Cl_2). ^1H NMR (400 MHz, CDCl_3) δ 7.85 (m, 2H), 7.45 (m, 2H), 7.13 (m, 2H), 6.82 (m, 2H), 4.03 (s, 2H). mass spec (FAB, $M+1$) 319 m/e.

20

EXAMPLE 19

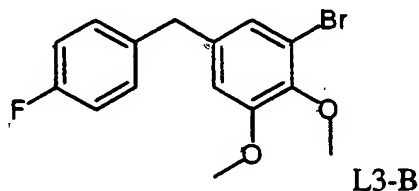
4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-butyric acid L3

- 25 Step 1: (3-Bromo-4,5-dimethoxy-phenyl)-(4-fluoro-phenyl)-methanol L3-A



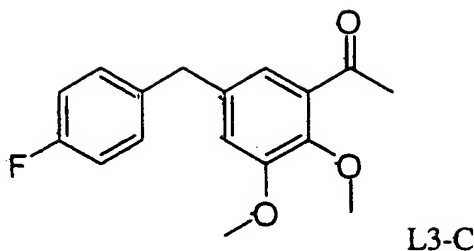
In a dried round bottom flask under argon, 1.0 M 4-fluorophenyl-magnesium bromide in THF (25.5 mL, 25.5 mmol) was slowly added to 5-bromoveratraldehyde (2.5 g, 10.2 mmol) in dry THF (150 mL) at 0°C. The resulting solution was stirred for 15 minutes then allowed to stir at room temperature for 2 hours. The solvent was then removed *in vacuo* and the residue was partitioned between 10 % KHSO₄ solution and EtOAc. The aqueous layer was extracted three times with EtOAc and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to a yellow oil. The crude product was taken on without further purification. ¹H NMR (400 MHz, CDCl₃) δ 7.33 (m, 2H), 7.05 (m, 3H), 6.86 (m, 1H), 5.74 (s, 1H), 3.83 (s, 6H).

Step 2: Preparation of L3-B



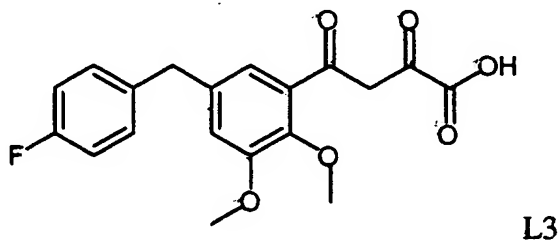
To (3-bromo-4,5-dimethoxy-phenyl)-(4-fluoro-phenyl)-methanol (2.95 g, 8.65 mmol) in dry CH₂Cl₂ at 0°C was added triethylsilane (3.54 mL, 22.2 mmol) and borontrifluoride diethyl etherate (2.27 mL, 22.2 mmol). The solution was allowed to stir overnight at room temperature. The solvent was then removed *in vacuo* and the residue was partitioned between sat. NaHCO₃ solution and CH₂Cl₂. The aqueous layer was extracted three times with CH₂Cl₂ and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated to a clear oil. The crude product was chromatographed on silica gel using 10 % EtOAc / hexane as the elutant. Collected and concentrated pure product fractions to give afford L3-B as a clear oil. R_f = 0.41 (10 % EtOAc / hexane). ¹H NMR (400 MHz, CDCl₃) δ 7.13 (m, 2H), 6.97 (m, 3H), 6.62 (m, 1H), 3.86 (s, 2H), 3.83 (s, 3H), 3.81 (s, 3H).

Step 3: 1-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-ethanone L3-C



In dried glassware under argon, slowly added 2.5 M *n*-BuLi in hexane to L3-B (2.50 g, 7.69 mmol) in distilled THF (45 mL) at -78°C. Aged solution 10 minutes then added *N*-methoxy-*N*-methylacetamide (1.11 mL, 10.8 mmol) dropwise. The reaction was stirred for 30 minutes then allowed to slowly warm to room temperature over 2 hours. The reaction was quenched with sat. NH₄Cl solution and extracted three times with EtOAc. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated to a yellow oil. The crude product was chromatographed on silica gel using 5 % EtOAc / hexane as elutant. Collected and concentrated product fractions to afford L3-C as a clear oil. R_f = 0.27 (10 % EtOAc / hexane).
¹H NMR (400 MHz, CDCl₃) δ 7.12 (m, 2H), 7.05 (m, 1H), 6.97 (m, 2H), 6.80 (m, 1H), 3.90 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H), 2.61 (s, 3H).

Step 4: 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-butyrlic acid L3



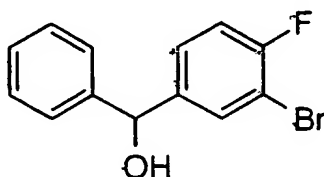
In a manner similar to example AIV-2-1, 4-[5-(4-fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-butyrlic acid ethyl ester was formed and the crude material was hydrolyzed in a manner similar to example AIV-3-1 using 1N NaOH to afford L3 as a yellow solid. R_f = 0.67 (6:6:94 MeOH / AcOH / CH₂Cl₂). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (s, 1H), 7.25 (m, 1H),

7.14 (m, 2H), 7.00 (m, 2H), 6.88 (m, 1H), 3.94 (s, 2H), 3.90 (s, 3H), 3.85 (s, 3H). mass spec (FAB, M+1) 361 m/e.

EXAMPLE 20

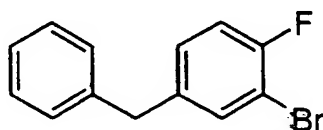
5 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyric acid W1

Step 1: (3-Bromo-4-fluorophenyl)phenylmethanol W1-A



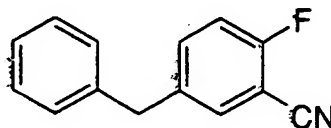
To a cold (0 °C) solution of 3-bromo-4-fluorobenzaldehyde (25.5 g) in THF
10 (300 mL) under an atmosphere of argon, a solution of phenylmagnesium
bromide in diethyl ether (3 M, 45 mL) was added. The resultant solution
was stirred at room temp. for 2.5 h, and treated with aq. HCl. The
resultant mixture was diluted with ethyl acetate, and neutralized with
aq. HCl. The organic extract was dried over magnesium sulfate,
15 filtered, and concentrated under vacuum to provide the title alcohol.

Step 2: 1-Benzyl-3-bromo-4-fluorobenzene W1-B



To a cold (0 °C) solution of (3-bromo-4-fluorophenyl)phenylmethanol (35
20 g) and triethylsilane (100 g) in dichloromethane (400 mL), boron
trifluoride diethyl etherate (24 mL) was added dropwise over a period of
45 min. The resultant mixture was stirred at 0 °C for 1 hr, diluted with
dichloromethane, and neutralized with saturated aq. sodium
bicarbonate. The organic extract was washed with brine, dried over
25 magnesium sulfate, filtered, and concentrated under vacuum. The
residue was subjected to column chromatography on silica gel eluted
with hexane. Collection and concentration of appropriate fractions
provided the title bromide.

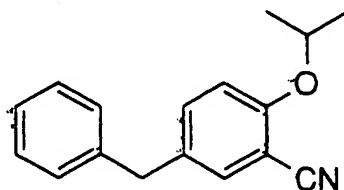
Step 3: 5-Benzyl-2-fluorobenzonitrile W1-C



To a mixture of 1-benzyl-3-bromo-4-fluorobenzene (14.7 g) and zinc
5 cyanide (38.7 g) in dimethylformamide (55 mL), purged with a steady
stream of argon for 45 min., tetrakis(triphenylphosphine)palladium(0) (7
g) was added. The resultant mixture was stirred at 95 °C for 2 days
under an atmosphere of argon. The resultant mixture was diluted with
ethyl acetate, washed successively with water, aq. HCl, and brine. The
10 organic extract was dried over magnesium sulfate, filtered, and
concentrated under vacuum. The residue was subjected to column
chromatography on silica gel eluted with 5 - 25% ethyl acetate - hexane
gradient. Collection and concentration of appropriate fractions provided
the title nitrile.

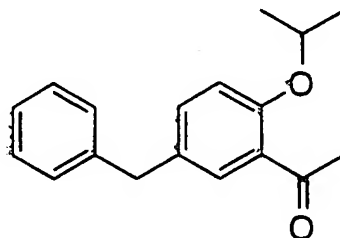
15

Step 4: 5-Benzyl-2-isopropoxybenzonitrile W1-D



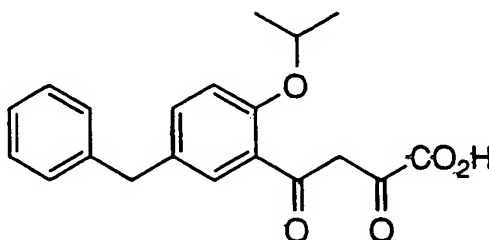
To a mixture of 5-benzyl-2-fluorobenzonitrile (0.55 g) and isopropyl
alcohol (0.22 mL) in THF (15 mL) at room temp., a solution of potassium
20 bis(trimethyl-silyl)amide (0.5 M, 7 mL) in toluene was added. The
resultant mixture was stirred at room temp. for 2 days under an
atmosphere of argon. The resultant mixture was diluted with ethyl
acetate, washed successively with aq. NH₄Cl, and brine. The organic
extract was dried over magnesium sulfate, filtered, and concentrated
25 under vacuum. The residue was subjected to column chromatography
on silica gel eluted with 10% ethyl acetate in hexane. Collection and
concentration of appropriate fractions provided the title nitrile.

Step 5: 5-Benzyl-2-isopropoxyacetophenone W1-E



To a solution of 5-benzyl-2-isopropoxybenzonitrile (0.6 g) in benzene (15
5 mL), a solution of methylmagnesium iodide (3 M, 1.45 mL) in ether was
added. The resultant mixture was heated at 80 °C overnight under an
atmosphere of argon. The resultant mixture was treated with aq. HCl
and washed with brine. The organic extract was dried over magnesium
sulfate, filtered, and concentrated under vacuum. The residue was
10 subjected to column chromatography on silica gel eluted with 10% ethyl
acetate in hexane. Collection and concentration of appropriate fractions
provided the title ketone.

Step 6: 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutanoic acid W1



15

To a solution of 5-benzyl-2-isopropoxyacetophenone (0.268 g) and
dimethyl oxalate (0.315 g) in THF (10 mL) at room temp., sodium
methoxide (85 mg) was added. The resultant mixture was stirred at
room temp. for 2 hr. under an atmosphere of argon. The resultant
20 mixture was treated with aq. NaOH (1M, 5.5 mL) and stirred at room
temp for 1 hr. The product solution was diluted with ethyl acetate,
washed successively with aq. HCl and brine. The organic extract was
dried over magnesium sulfate, filtered, and concentrated under
vacuum. The residual oil was triturated with a mixture of ether and

hexane. The yellow solid precipitated was filtered to provide the title product. ^1H NMR (CDCl_3) δ 7.8-6.8 (m, 9H), 4.6 (m, 1H), 3.95 (s, 2H), 1.43 (d, 6H).

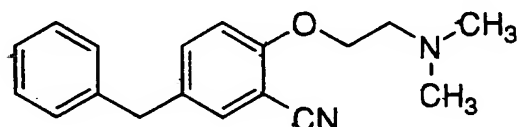
5

EXAMPLE 21

4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-dioxobutyric acid
W2

Step 1: 5-Benzyl-2-(2-N,N-dimethylaminoethoxy)benzonitrile W2-A

10

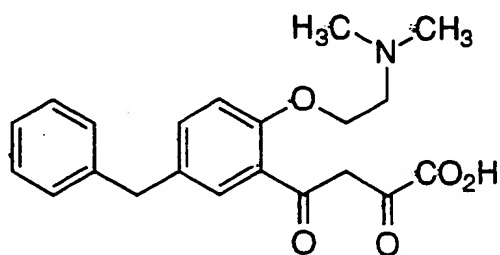


15

20

To a mixture of 5-benzyl-2-fluorobenzonitrile (0.60 g) and N,N-dimethylethanolamine (0.32 mL) in THF (20 mL) at room temp., a solution of potassium bis(trimethylsilyl)amide (0.5 M, 6.25 mL) in toluene was added. The resultant mixture was heated at 60 °C overnight under an atmosphere of argon. The resultant mixture was diluted with ethyl acetate, washed with brine. The organic extract was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with 5% methanol in chloroform. Collection and concentration of appropriate fractions provided the title nitrile.

Step 2: 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-dioxo-butyric acid W2



25

The title compound was prepared using the protocol described in Example W1, Step 5 - 6 substituting 5-benzyl-2-isopropoxybenzonitrile

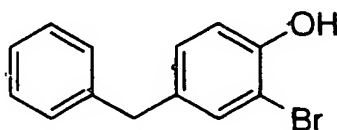
with 5-Benzyl-2-(2-N,N-dimethylaminoethoxy)benzonitrile in Step 5. ^1H NMR ($\text{DMSO}-d_6$) δ 7.7-6.9 (m, 9H), 4.45 (br s, 2H), 3.98 (s, 2H), 3.5 (br s, 2H), 2.85 (s, 6H).

5

EXAMPLE 22

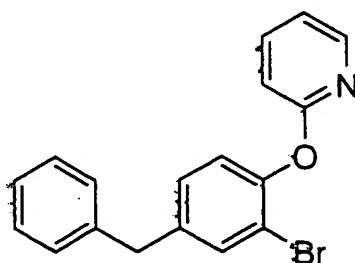
4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid W3

Step 1: 4-Benzyl-2-bromophenol W3-A



- 10 To a solution of 4-hydroxydiphenylmethane (10 g) in chloroform (60 mL) at room temp., a solution of bromine (2.9 mL) in chloroform (20 mL) was added dropwise over a period of 2 hr. The resultant mixture was stirred at room temp. overnight, diluted with chloroform, and washed successively with sat. aq. sodium bicarbonate and brine. The organic
15 extract was dried over magnesium sulfate, filtered, and concentrated under vacuum to provide the title compound.

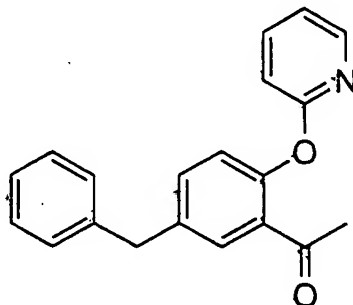
Step 2: 5-Benzyl-2-(pyridin-2-yloxy)phenyl bromide W3-B



- 20 A mixture of 4-benzyl-2-bromophenol (3 g) and sodium hydride (0.3 g) in DMSO (60 mL) was stirred at room temp. until evolution of gas subsided. The resultant mixture was treated with 2-fluoropyridine (2 mL) and stirred at 150 °C under an atmosphere of argon overnight. The product mixture was partitioned between chloroform and water. The organic
25 extract was washed successively with water and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue

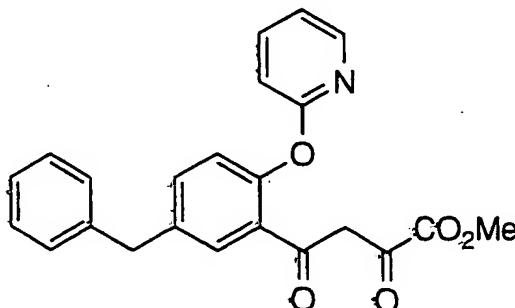
was subjected to column chromatography on silica gel eluting with chloroform. Collection and concentration of appropriate fractions provide the title bromide.

5 Step 3: 5-Benzyl-2-(pyridin-2-yloxy)acetophenone W3-C



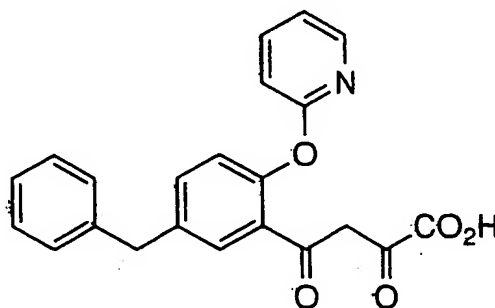
To a cold (-78 °C) solution of 5-benzyl-2-(pyridin-2-yloxy)phenyl bromide (1.68 g) in diethyl ether (40 mL), a solution of n-BuLi in hexanes (2.5 M, 2.12 mL) was added. The resultant mixture was stirred at -78 °C for 1 h
10 and was treated with N-methoxy-N-methylacetamide (0.6 mL). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at room temp. overnight. The product mixture was diluted with ether and partitioned with aq. HCl. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under
15 vacuum. The residue was subjected to column chromatography on silica gel eluting with chloroform. Collection and concentration of appropriate fractions provide the title ketone.

20 Step 4: Methyl 4-[5-benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-
 butyrate W3-D



To a cold (-78 °C) solution of 5-benzyl-2-(pyridin-2-yloxy) acetophenone (0.3 g) in THF (15 mL), a solution of LDA in heptane and THF (2 M, 0.56 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with a solution of dimethyl oxalate (0.213 g) in THF. The reaction mixture was allowed to warm up slowly to room temp. and was stirred at room temp. overnight. The product mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residual oil was triturated with diethyl ether. The resultant ethereal solution was isolated and concentrated under vacuum to provide the title ester.

Step 5: 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid
W3



15

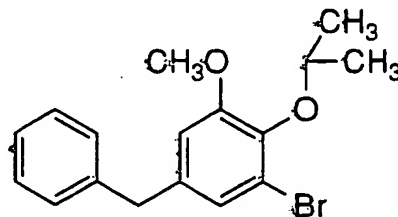
To a solution of methyl 4-[5-benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyrate (0.14 g) in THF (10 mL) at room temp., aq. NaOH (1 M, 0.44 mL) was added. The resultant mixture was stirred at room temp for 6 h. The product mixture was diluted with chloroform and partitioned with aq. HCl. The organic extract was washed with brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was triturated with a mixture of diethyl ether and hexane. Filtration of the resultant solid provided the title acid. ¹H NMR (CDCl₃) δ 8.25 (m, 1H), 7.8-6.8 (m, 12H), 4.05 (s, 2H).

25

EXAMPLE 23

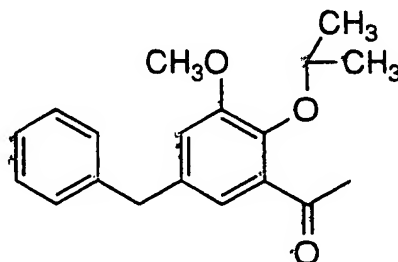
4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric acid W4

Step 1: 5-Benzyl-2-isopropoxy-3-methoxy-1-bromobenzene W4-A



A mixture of 4-benzyl-2-bromo-6-methoxyphenol (0.5 g), cesium carbonate (0.84 g), and isopropyl iodide (0.51 mL) in DMF (2 mL) was stirred at room temp. overnight. The reaction mixture was diluted with ether, and washed with aq. ammonium chloride. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 5% ethyl acetate in hexane. Collection and concentration of appropriate fractions provide the title bromide.

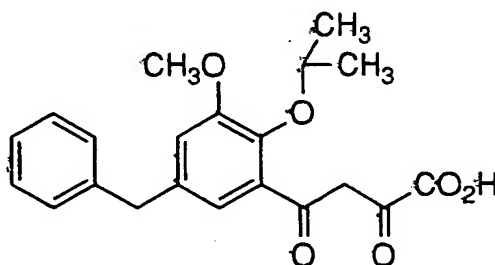
Step 2: 5-Benzyl-2-isopropoxy-3-methoxy-acetophenone W4-B



To a mixture of 5-benzyl-2-isopropoxy-3-methoxy-1-bromobenzene (0.4 g), thallium acetate (0.41 g), 1,3-bis(diphenylphosphino)propane (0.138 g) and triethylamine (0.67 mL) in DMF (3 mL) in a pressure tube, purged with argon for a period of 5 minute, palladium acetate (67.2 mg) and n-butyl vinyl ether (0.77 mL) was added. The reaction tube was sealed and stirred at 100 °C overnight. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (5 mL) and treated with aq. HCl (1M, 2.5 mL). The resultant mixture was stirred at rt for 1 hr., diluted with ether, and washed with brine. The organic extract was dried over magnesium sulfate, filtered, and concentrated under

vacuum. The residue was subjected to column chromatography on silica gel eluting with 10% ethyl acetate in hexane. Collection and concentration of appropriate fractions provide the title ketone.

5 Step 3: 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric acid W4



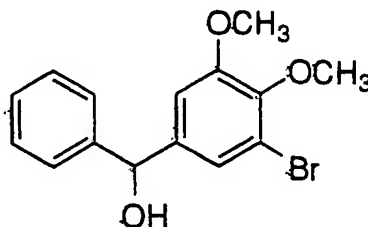
To a solution of 5-benzyl-2-isopropoxy-3-methoxy-acetophenone (79 mg) and dimethyl oxalate (125 mg) in THF (2 mL), sodium methoxide (30 mg)
 10 was added. The resultant mixture was stirred at room temp. for 0.5 h under an atmosphere of argon. The resultant mixture was diluted with THF (3 mL) and methanol (0.5 mL), and treated with aq. NaOH (1M, 3 mL) and stirred at room temp for 1 hr. The product solution was adjusted to pH 2 with addition of aq. HCl. The resultant mixture was
 15 concentrated under vacuum. The residue was subjected to HPLC purification on reverse phase stationary phase. Collection and lyophilization of appropriate fractions provide the title product as light yellow solid. ¹H NMR (CDCl₃) δ 7.58-6.89 (m, 8H), 4.53 (m, 1H), 3.97 (s, 2H), 3.81 (s, 3H), 1.26 (d, 6H).

20

EXAMPLE 24

4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid W5

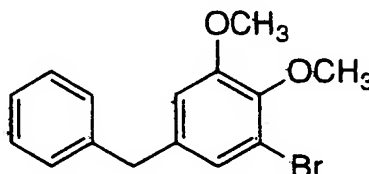
Step 1: (3-Bromo-4,5-dimethoxyphenyl)phenylmethanol W5-A



25

To a cold (0 °C) solution of 3-bromo-4,5-dimethoxybenzaldehyde (5.42 g) in THF (25 mL) under an atmosphere of argon, a solution of phenylmagnesium bromide in THF (1 M, 25 mL) was added. The resultant solution was stirred at room temp. for 1 h, and treated with aq. HCl. The resultant mixture was diluted with ether, and neutralized with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum to provide the title alcohol.

10 Step 2: 5-Benzyl-2,3-dimethoxy-1-bromobenzene W5-B

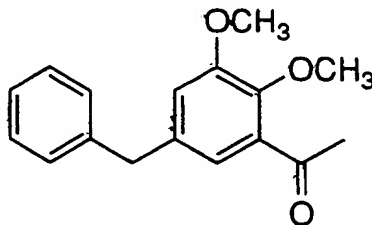


To a cold (0 °C) solution of the (3-Bromo-4,5-dimethoxyphenyl)phenyl-methanol (5 g) and triethylsilane (3.7 g) in dichloromethane (80 mL), boron trifluoride diethyl etherate (3 mL) was added dropwise over a period of 5 min. The resultant mixture was stirred at room temp. for 1 hr, diluted with dichloromethane, and neutralized with saturated aq. sodium bicarbonate. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel.

15

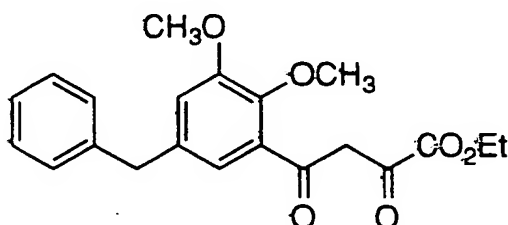
20 Collection and concentration of appropriate fractions provided the title bromide.

Step 3: 5-Benzyl-2,3-dimethoxyacetophenone W5-C



To a cold (-78 °C) solution of 5-benzyl-2,3-dimethoxy-1-bromobenzene (3.1 g) in THF (46 mL), a solution of n-BuLi in hexanes (2.5 M, 4.2 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with N-methoxy-N-methylacetamide (1.1 g). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at room temp. 1 h. The product mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with a 5 - 20% ethyl acetate gradient. Collection and concentration of appropriate fractions provide the title ketone.

Step 4: Ethyl 4-(5-benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyrates
W5-D

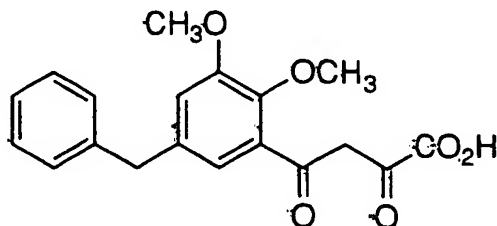


15

To a solution of 5-benzyl-2,3-dimethoxyacetophenone (0.55 g) and diethyl oxalate (0.48 g) in THF (8 mL), sodium ethoxide (0.22 g) was added. The resultant mixture was stirred at room temp. for 1 hr under an atmosphere of argon. The reaction mixture was quenched with aq. KHSO4, and diluted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum to provide the title ester.

20

Step 5: 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid W5

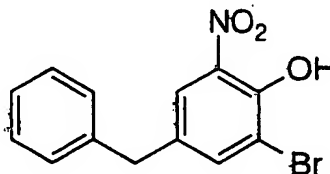


25

To a solution of ethyl 4-(5-benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyrate (0.59 g) in ethanol (8 mL), aq. NaOH (1 M, 6.4 mL) was added. The resultant mixture was stirred at room temp for 2 h. The product mixture was concentrated under vacuum. The residue was partitioned
5 between ethyl acetate and aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was triturated with a mixture of diethyl ether and hexane. Filtration of the resultant solid provided the title acid. ¹H NMR (CDCl₃) δ 7.4-7.2 (m, 7H), 6.92 (br s, 1H), 3.97 (s, 2H), 3.89 (s, 3H), 3.84 (s,
10 3H).

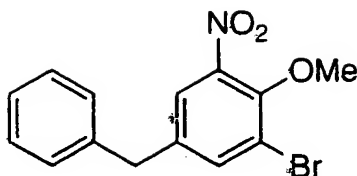
EXAMPLE 25

4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-dioxobutyric acid W6

15 Step 1: 4-benzyl-2-bromo-6-nitrophenol W6-A

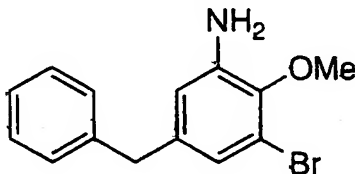
To a solution of 4-benzyl-2-bromophenol (7.2 g) in glacial acetic acid (65 mL) at room temp., a solution of conc. nitric acid (15.8 M, 1.7 mL) in glacial acetic acid (10 mL) was added dropwise over a period of 1 hr. The
20 resultant solution was stirred at room temp. for 2 hr., poured into ice-water, and neutralized with aq. ammonia. The mixture was extracted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting
25 with a gradient of 5 - 7% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title phenol.

Step 2: 5-Benzyl-2-methoxy-3-nitro-1-bromobenzene W6-B



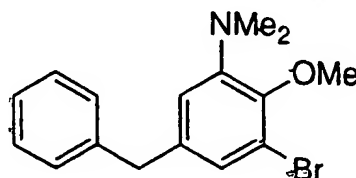
To a cold (0 °C) solution of 4-benzyl-2-bromo-6-nitrophenol (1.3 g) in diethyl ether (50 mL), a solution of diazomethane in diethyl ether was added over a period of 15 minute. The diazomethane solution was
5 prepared by addition of 1-methyl-3-nitro-1-nitrosoguanidine (2.0 g) portionwise into a mixture of 40% aq. KOH (50 mL) and ether (50 mL) at 0 °C over a period of 15 min. The resultant solution was stirred at room temp. overnight, and concentrated under vacuum. The residue was
10 subjected to column chromatography on silica gel eluting with 4% ethyl acetate in hexane. Collection and concentration of appropriate fractions provide the title bromide.

Step 3: 5-Benzyl-2-methoxy-3-bromoaniline W6-C



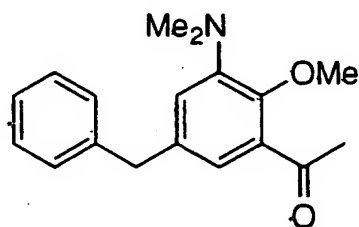
15 A mixture of 5-benzyl-2-methoxy-3-nitro-1-bromobenzene (2.0 g) and 5% Pt on charcoal (0.2 g) in a mixture of ethanol (100 mL) and acetic acid (5 mL) was shaken in a Parr hydrogenator under an atmosphere of hydrogen gas (56 psi) at room temp. for 45 min. The resultant mixture was filtered through a plug of CELITE diatomaceous earth. The filtrate
20 was concentrated under vacuum to provide the title aniline.

Step 4: 5-Benzyl-2-methoxy-3-bromo-N,N-dimethylaniline W6-D



To a solution of 5-benzyl-2-methoxy-3-bromoaniline (1.9 g), formaldehyde (37%, 5.3 g), and sodium cyanoborohydride (1.25 g) in acetonitrile (40 mL) at room temp, glacial acetic acid (2 mL) was added dropwise over a period of 3 hr. The reaction mixture was stirred at room temp.
5 overnight. The resultant solution was adjusted to pH ~6 with addition of aq sodium bicarbonate and partitioned with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 3% ethyl acetate in hexane.
10 Collection and concentration of appropriate fractions provide the title bromide.

Step 5: 5-Benzyl-2-methoxy-3-N,N-dimethylaminoacetophenone
W6-E

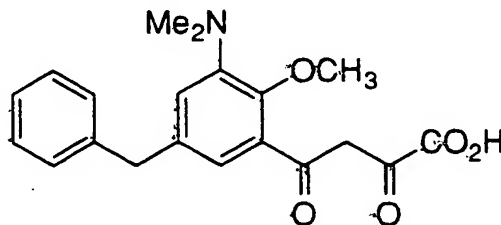


15

To a mixture of 5-benzyl-2-methoxy-3-bromo-N,N-dimethylaniline (0.33 g), thallium acetate (0.3 g), 1,3-bis(diphenylphosphino)propane (0.106 g) and triethylamine (0.42 mL) in DMF (2.5 mL) in a pressure tube, purged with argon for a period of 5 minute, palladium acetate (56 mg) and n-butyl vinyl ether (0.67 mL) was added. The reaction tube was sealed and stirred at 100 °C for 1 hr. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (10 mL) and treated with aq. HCl (1M, 3 mL). The resultant mixture was stirred at rt for 1 hr.,
20 diluted with ether, basified with aq. sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 4% ethyl acetate in hexane. Collection and concentration of appropriate fractions provide the title ketone.

30

Step 6: 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-dioxobutyric acid W6

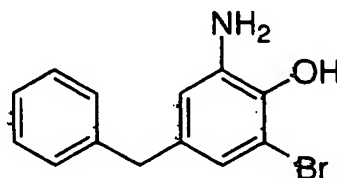


To a solution of 5-benzyl-2-methoxy-3-N,N-dimethylaminoacetophenone (75 mg) and diethyl oxalate (57 mg) in THF (2 mL), sodium ethoxide (36 mg) was added. The resultant mixture was stirred at room temp. for 1 hr. under an atmosphere of argon. The reaction mixture was diluted with ethyl acetate and partitioned with 5% aq. KHSO₄. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in ethanol (3 mL) and treated with aq. NaOH (1M, 1 mL) and stirred at room temp for 1 hr. The product solution was concentrated under vacuum. The residue was dissolved in acetonitrile and acidified with aq TFA, and subjected to HPLC purification on reverse phase. Collection and lyophilization of appropriate fractions provided the title acid. ¹H NMR (CDCl₃) δ 7.6-7.0 (m, 8H), 4.00 (s, 2H), 3.89 (s, 3H), 3.21 (s, 6H).

EXAMPLE 26

4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-butyric acid W7

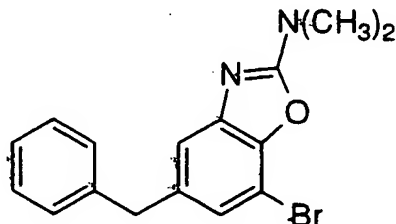
Step 1: 3-Benzyl-5-bromo-6-hydroxyaniline W7-A



To a solution of 4-benzyl-2-bromo-6-nitrophenol (8.65 g) and 5% Pt on charcoal (0.15 g) in a mixture of ethanol (100 mL) and acetic acid (8 mL) was shaken in a Parr hydrogenator under an atmosphere of hydrogen

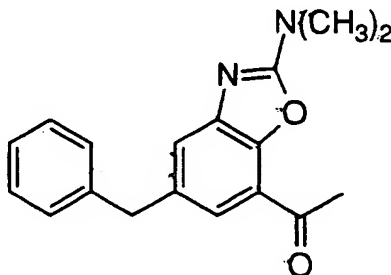
gas (43 psi) at room temp. for 1 hr. The resultant mixture was filtered through a plug of CELITE diatomaceous earth. The filtrate was concentrated under vacuum to provide the title aniline.

5 Step 2: 5-Benzyl-7-bromo-2-N,N-dimethylaminobenzoxazole W7-B



A mixture of 3-benzyl-5-bromo-6-hydroxyaniline (1.0 g) and anhydrous (dichloromethylene)dimethylammonium chloride (0.6 g; dried by repetitive concentration from toluene under vacuum) in anhydrous
10 chloroform (30 mL) was heated under reflux overnight under an atmosphere of argon. The reaction mixture was diluted with chloroform, and washed successively with aq. KOH and brine. The organic extract was dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography
15 on silica gel eluting with 40% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title benzoxazole.

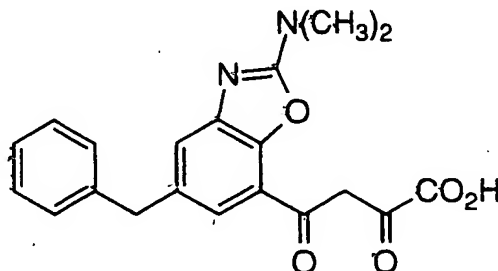
Step 3: 7-Acetyl-5-benzyl-2-N,N-dimethylaminobenzoxazole W7-C



20 To a mixture of 5-benzyl-7-bromo-2-N,N-dimethylaminobenzoxazole (0.8 g), thallium acetate (0.695 g), 1,3-bis(diphenylphosphino)propane (0.25 g) and triethylamine (0.98 mL) in DMF (5 mL) in a pressure tube, purged with argon for a period of 15 minute, palladium acetate (130 mg) and n-

butyl vinyl ether (1.55 mL) was added. The reaction tube was sealed and stirred at 100 °C overnight. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (20 mL) and treated with aq. HCl (1M, 6 mL). The resultant mixture was stirred at rt for 1 hr., diluted with ether, basified with aq. sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title ketone.

Step 4: 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-
butyric acid W7



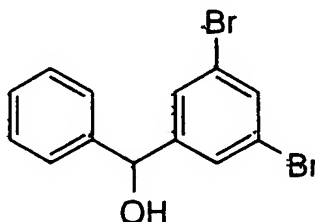
To a solution of 7-acetyl-5-benzyl-2-N,N-dimethylaminobenzoxazole (200 mg) and diethyl oxalate (150 mg) in THF (7 mL), sodium ethoxide (138 mg) was added. The resultant mixture was stirred at room temp. for 3 hr. under an atmosphere of argon. The reaction mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was triturated with diethyl ether, and the solid precipitated was obtained by filtration. A solution of this intermediate ester (125 mg) in THF (4 mL) was treated with aq. NaOH (1M, 2.7 mL) and stirred at room temp for 1 hr. The product mixture was partitioned between ethyl acetate and aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was triturated with

ether. The yellow solid precipitated was filtered to provide the title acid.
1H NMR (CDCl₃) δ 7.54-7.16 (m, 8H), 4.05 (s, 2H), 3.25 (s, 6H).

EXAMPLE 27

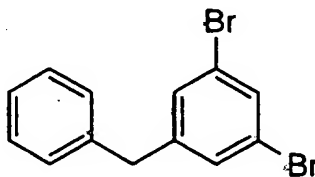
5 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric acid W8

Step 1: (3,5-dibromophenyl)phenylmethanol W8-A



To a cold (-78 °C) solution of 1,3,5-tribromobenzene (30 g) in diethyl ether
10 (500 mL), a solution of n-BuLi in hexanes (2.5 M, 38.1 mL) was added.
The resultant mixture was stirred at -78 °C for 1 h and was treated with
benzaldehyde (10.2 mL). The reaction mixture was allowed to warm up
slowly to 0 °C. and was stirred at that temp. for 1.5 hr. The product
mixture was diluted with ethyl acetate and partitioned with aq. HCl (1M,
15 95 mL). The organic extract was washed with brine, dried over
magnesium sulfate, filtered, and concentrated under vacuum to provide
the title alcohol.

Step 2: 1-Benzyl-3,5-dibromobenzene W8-B



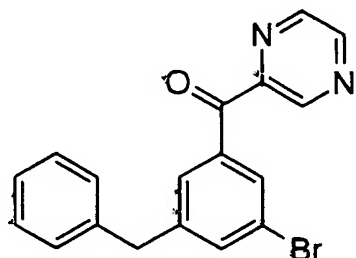
20

To a cold (0 °C) solution of (3,5-dibromophenyl)phenylmethanol (32.5 g)
and triethylsilane (27.7 g) in dichloromethane (500 mL), boron trifluoride
diethyl etherate (30 mL) was added dropwise over a period of 45 min.
The resultant mixture was stirred at 0 °C for 1 hr, and at room temp.
25 overnight. The product mixture was diluted with dichloromethane, and
neutralized with saturated aq. sodium bicarbonate. The organic extract

was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluted with hexane. Collection and concentration of appropriate fractions provided the title dibromide.

5

Step 3: (3-benzyl-5-bromophenyl) pyrazin-2-yl ketone W8-C



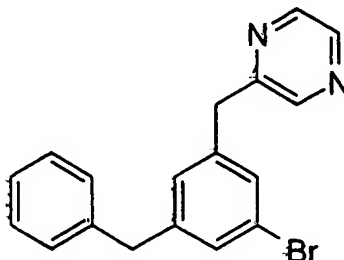
To a cold (-78 °C) solution of 1-benzyl-3,5-dibromobenzene (1.5 g) in diethyl ether (20 mL), a solution of n-BuLi in hexanes (2.5 M, 2 mL) was added.

10 The resultant mixture was stirred at -78 °C for 1 h and was treated with a solution of N-methoxy-N-methylpyrazinecarboxamide (0.84 g) in diethyl ether (5 mL). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at that temp. overnight. The product mixture was diluted with ethyl acetate and partitioned with aq.

15 HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 20% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title pyrazine.

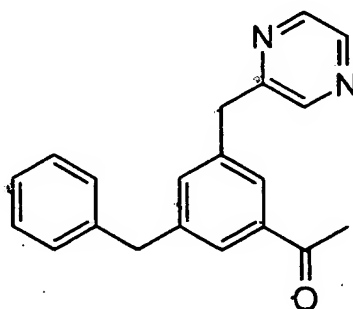
20

Step 4: 3-Benzyl-5-pyrazin-2-ylmethyl-1-bromobenzene W8-D



A mixture of (3-benzyl-5-bromophenyl) pyrazin-2-yl ketone (0.97 g) and anhydrous hydrazine (2 mL) in ethylene glycol (6 mL) was heated at 110 °C for 4 hr. Excess hydrazine was removed under reduced pressure. The residue ethylene glycol solution was treated with powdered solid
5 KOH (0.4 g) and heated under an atmosphere of argon for 4 h. The product mixture was partitioned between benzene and water. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to
10 column chromatography on silica gel eluting with 20-30% ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the title bromide.

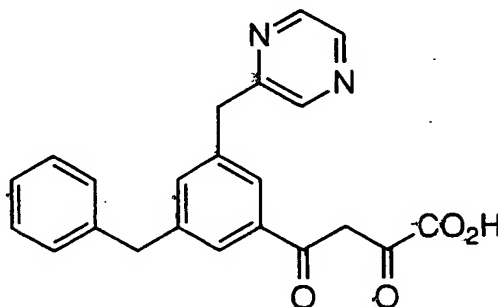
Step 5: 3-Benzyl-5-pyrazin-2-ylmethylacetophenone W8-E



15 To a mixture of 3-benzyl-5-pyrazin-2-ylmethyl-1-bromobenzene (0.77 g), thallium acetate (0.66 g), 1,3-bis(diphenylphosphino)propane (0.263 g) and triethylamine (1.27 mL) in DMF (5 mL) in a pressure tube, purged with argon for a period of 10 minute, palladium acetate (128 mg) and n-butyl vinyl ether (1.5 mL) was added. The reaction tube was sealed and
20 stirred at 100 °C overnight. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (5 mL) and treated with aq. HCl (3M, 4 mL). The resultant mixture was stirred at rt for 3 hr.,
25 diluted with ethyl acetate, basified with aq. sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane.

Collection and concentration of appropriate fractions provided the title ketone.

5 Step 6: 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric acid W8



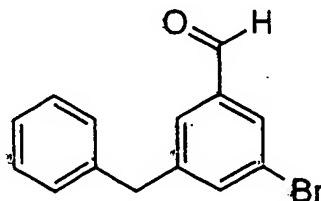
To a cold (-78 °C) solution of 3-benzyl-5-pyrazin-2-ylmethylacetophenone (0.595 g) in THF (4 mL), a solution of lithium bis(trimethylsilyl)amide in THF (1 M, 1.2 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with diethyl oxalate (0.18 mL). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at room temp. overnight. The product mixture was treated with aq. NaOH (1 M, 2 mL) and stirred at room temp for 4 h. The product solution was concentrated under vacuum. The residue was dissolved in acetonitrile and acidified with aq TFA, and subjected to HPLC purification on reverse phase. Collection and lyophilization of appropriate fractions provided the title acid. ¹H NMR (CDCl₃) δ 8.7-7.0 (m, 12H), 4.22 (s, 2H), 4.02 (s, 2H).

20

EXAMPLE 28

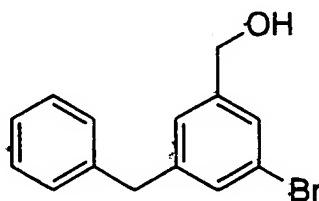
4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-dioxobutyric acid W9

Step 1: 3-Benzyl-5-bromobenzaldehyde W9-A



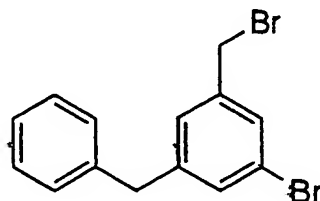
To a cold (-78 °C) solution of 1-benzyl-3,5-dibromobenzene (1.15 g) in THF (30 mL), a solution of n-BuLi in hexanes (2.5 M, 2 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with anhydrous DMF (0.3 mL). The reaction mixture was allowed to warm
5 up slowly to room temp. and was stirred at that temp. overnight. The product mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The
10 residue was subjected to column chromatography on silica gel eluting with 10% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title benzaldehyde.

Step 2: 3-Benzyl-5-bromobenzyl alcohol W9-B



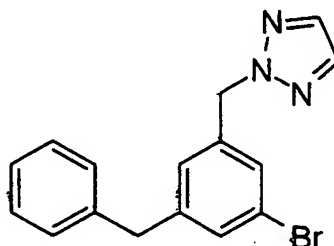
15 To a cold (0 °C) solution of 3-benzyl-5-bromobenzaldehyde (0.465 g) in methanol (5 mL), sodium borohydride (0.123 g) was added. The reaction mixture was stirred at room temp. for 3 hr. The product mixture was concentrated, and the residue partitioned between ethyl acetate and aq. HCl. The organic extract was washed with brine, dried over
20 magnesium sulfate, filtered, and concentrated under vacuum to provide the title alcohol.

Step 3: 3-Benzyl-5-bromobenzyl bromide W9-C



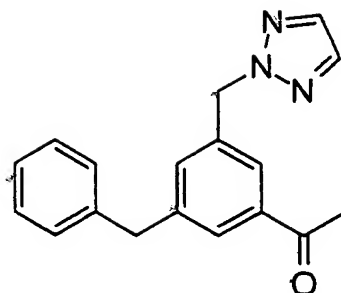
To a cold (0 °C) solution of 3-benzyl-5-bromobenzyl alcohol (0.32 g) and carbon tetrabromide (0.57 g) in dichloromethane (6 mL), a solution of triphenylphosphine (0.45 g) in dichloromethane (4 mL) was added dropwise. The reaction mixture was stirred at room temp. for 2 hr. The product mixture was concentrated, and the residue was subjected to column chromatography on silica gel eluting with 15% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title dibromide.

Step 4: 3-Benzyl-5-[1,2,3]triazol-2-ylmethyl-1-bromobenzene W9-D



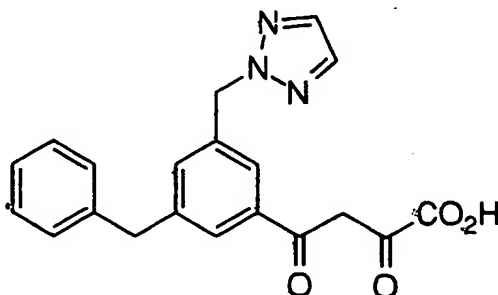
A mixture of sodium hydride (28 mg, 60% dispersion in mineral oil, washed with hexane) and 1,2,3-triazole (0.38 mL) in DMF was stirred at room temp. for 10 min. The resultant mixture was treated with a solution of 3-benzyl-5-bromobenzyl bromide in DMF. The reaction mixture was stirred at room temp. overnight. The product mixture was concentrated, and the residue partitioned between ethyl acetate and aq. ammonium chloride. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane. Collection and concentration of earlier fractions ($R_f = 0.8$, silica gel, eluted with 50% ethyl acetate in hexane) provided the title triazole bromide [^1H NMR (CDCl_3) δ 7.63 (s, 2H)], and later fractions ($R_f = 0.2$) provided the isomeric 3-benzyl-5-[1,2,3]triazol-1-ylmethyl-1-bromo-benzene analog [^1H NMR (CDCl_3) δ 7.76 (br s, 1H), 7.73 (br s, 1H)].

Step 5: 3-Benzyl-5-[1,2,3]triazol-2-ylmethylacetophenone W9-E



To a mixture of 3-benzyl-5-[1,2,3]triazol-2-ylmethyl-1-bromobenzene (0.4 g), thallium acetate (0.35 g), 1,3-bis(diphenylphosphino)propane (0.13 g) and triethylamine (0.68 mL) in DMF (4 mL) in a pressure tube, purged
 5 with argon for a period of 10 minute, palladium acetate (55 mg) and n-butyl vinyl ether (0.8 mL) was added. The reaction tube was sealed and stirred at 100 °C overnight. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (5 mL) and treated with aq.
 10 HCl (3M, 4 mL). The resultant mixture was stirred at rt for 3 hr., diluted with ethyl acetate, basified with aq. sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane.
 15 Collection and concentration of appropriate fractions provided the title ketone.

Step 6: 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-dioxobutyric acid W9



20

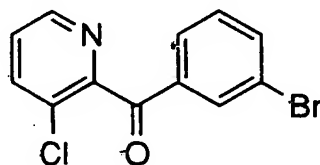
To a solution of 3-benzyl-5-[1,2,3]triazol-2-ylmethylacetophenone (60 mg) and diethyl oxalate (89 mg) in THF (3 mL), sodium ethoxide (21 mg) was

added. The resultant mixture was stirred at room temp. for 1 hr. under an atmosphere of argon. The reaction mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was dissolved in THF (1 mL) and treated with aq. NaOH (1M, 1 mL) and stirred at room temp for 3 hr. The product mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was triturated with hexane/ethyl acetate. Filtration and collection of the solid provided the title acid. $^1\text{H NMR}$ (CDCl_3) δ 7.78-7.10 (m, 11H), 5.64 (s, 2H), 4.03 (s, 2H).

EXAMPLE 29

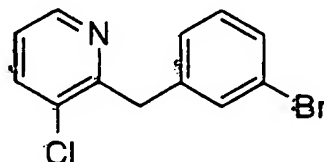
4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric acid W10

Step 1: 3-Chloropyridin-2-yl 3-bromophenyl ketone W10-A



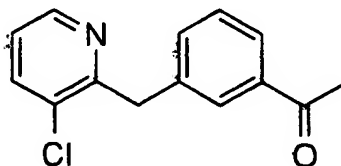
To a cold (-78 °C) solution of 1,3-dibromobenzene (0.8 mL) in THF (4 mL), a solution of n-BuLi in hexanes (2.5 M, 3.2 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with a solution of N-methoxy-N-methyl-3-chloropyridine-2-carboxamide in THF (4 mL). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at that temp. overnight. The product mixture was diluted with ethyl acetate and partitioned with aq. HCl. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 50% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title ketone.

Step 2: 3-(3-Chloropyridin-2-ylmethyl)-1-bromobenzene W10-B



A mixture of 3-chloropyridin-2-yl 3-bromophenyl ketone (0.2 g) and anhydrous hydrazine (1 mL) in ethylene glycol (2.5 mL) was heated at 110 °C for 4 hr. Excess hydrazine was removed under reduced pressure. The residue ethylene glycol solution was treated with powdered solid KOH (0.1 g) and heated under an atmosphere of argon for 1 h. The product mixture was partitioned between benzene and water. The organic extract was washed with brine, dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 25% ethyl acetate. Collection and concentration of appropriate fractions provided the title bromide. ¹H NMR (CDCl₃) δ 8.47 (br dd, 1H), 7.66 (br dd, 1 H), 7.44 (br s, 1H), 7.35 (br d, 1 H), 7.22 (br d, 1H), 7.16-7.12 (m 2 H), 4.28 (s, 2H).

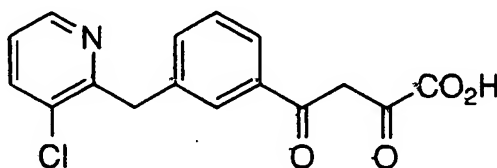
Step 3: 3-(3-Chloropyridin-2-ylmethyl)acetophenone W10-C



To a mixture of 3-(3-chloropyridin-2-ylmethyl)-1-bromobenzene (0.76 g), thallium acetate (0.87 g), 1,3-bis(diphenylphosphino)propane (0.27 g) and triethylamine (1.67 mL) in DMF (6 mL) in a pressure tube, purged with argon for a period of 10 minute, palladium acetate (134 mg) and n-butyl vinyl ether (1.96 mL) was added. The reaction tube was sealed and stirred at 100 °C for 2 days. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (3 mL) and treated with aq. HCl (3M, 3 mL). The resultant mixture was stirred at room temp. overnight, diluted with ethyl acetate, basified with aq. sodium

bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 25% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title ketone.

Step 4: 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric acid W10

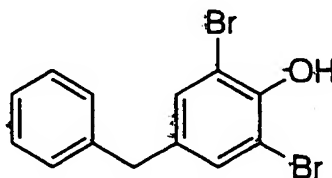


To a cold (-78 °C) solution of 3-(3-chloropyridin-2-ylmethyl)acetophenone (0.19 g) in THF (3 mL), a solution of lithium bis(trimethylsilyl)amide in hexane (1 M, 1.54 mL) was added. The resultant mixture was stirred at -78 °C for 1 h and was treated with diethyl oxalate (0.22 mL). The reaction mixture was allowed to warm up slowly to room temp. and was stirred at room temp. for 1.5 hr. The product mixture was treated with aq. NaOH (1 M, 3.2 mL) and stirred at room temp overnight. The product solution was concentrated under vacuum. The residue was dissolved in acetonitrile and acidified with aq TFA, and subjected to HPLC purification on reverse phase. Collection and lyophilization of appropriate fractions provided the title acid. ¹H NMR (DMSO-*d*₆) δ 8.48 (br d, 1H), 7.92 - 7.0 (m, 7H), 4.35 (s, 2H).

EXAMPLE 30

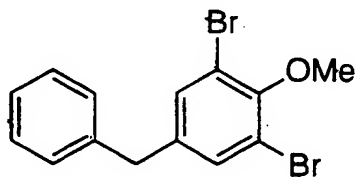
4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)phenyl]-2,4-dioxobutyric acid W11

Step 1: 4-Benzyl-2,6-dibromophenol W11-A



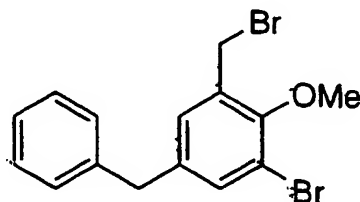
To a solution of 4-hydroxydiphenylmethane (15.3 g) in glacial acetic acid (200 mL) at room temp., a solution of bromine (8.6 mL) in acetic acid (20 mL) was added dropwise over a period of half an hour. The resultant mixture was stirred at room temp. for 3 hr, poured into ice water, and partitioned with toluene. The organic extract was washed successively with 10% aq. sodium hydrogensulfite and brine, dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 7% ethyl acetate in hexane. Collection and concentration of appropriate fractions provided the title dibromophenol.

Step 2: 4-Benzyl-2,6-dibromo-1-methoxybenzene W11-B



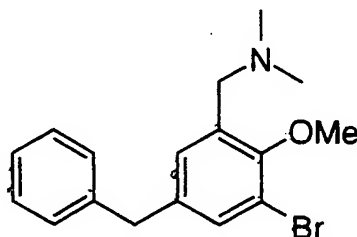
To a cold (0 °C) solution of 4-benzyl-2,6-dibromophenol (10 g) in diethyl ether (100 mL), a solution of diazomethane in diethyl ether was added over a period of 20 minutes. The diazomethane solution was prepared by addition of 1-methyl-3-nitro-1-nitrosoguanidine (8.5 g) portionwise into a mixture of 40% aq. KOH (100 mL) and ether (50 mL) at 0 °C over a period of 15 min. The resultant solution was stirred at room temp. for two days, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 1-2 % ethyl acetate in hexane gradient. Collection and concentration of appropriate fractions provided the title dibromide.

Step 3: 3-Benzyl-5-bromo-6-methoxybenzyl bromide W11-C



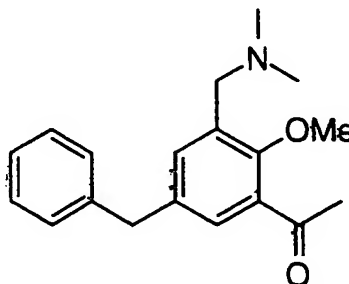
The title compound was prepared using the protocol described in Example W9, Step 1 - 3 substituting 1-benzyl-3,5-dibromobenzene with 4-benzyl-2,6-dibromo-1-methoxybenzene in Step 1.

5 Step 4: 3-Benzyl-1-bromo-5-N,N,-dimethylaminomethyl-6-methoxybenzene W11-D



10 A solution of 3-benzyl-5-bromo-6-methoxybenzyl bromide (0.65 g), dimethylamine hydrochloride (0.29 g), and diisopropylethylamine (0.61 mL) in acetonitrile (8 mL) was heated at 60 °C overnight. The resultant solution was concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 4 % methanol in chloroform. Collection and concentration of appropriate fractions provided the title bromide.

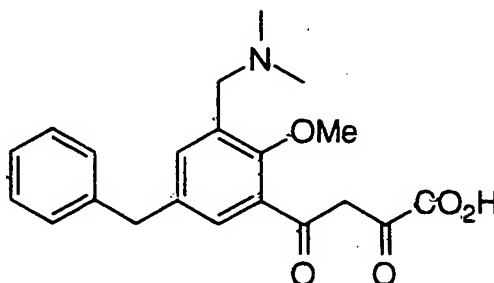
15 Step 5: 5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)-acetophenone W11-E



20 To a mixture of 3-benzyl-1-bromo-5-N,N,-dimethylaminomethyl-6-methoxybenzene (0.30 g), thallium acetate (0.28 g), 1,3-bis(diphenylphosphino)propane (0.80 g) and triethylamine (0.39 mL) in DMF (2 mL) in a pressure tube, purged with argon for a period of 5 minute, palladium acetate (43 mg) and n-butyl vinyl ether (0.62 mL) was added.

The reaction tube was sealed and stirred at 100 °C overnight. The reaction mixture was filtered through a bed of CELITE diatomaceous earth, and the filtrate concentrated under vacuum. The residue was dissolved in THF (10 mL) and treated with aq. HCl (1M, 3 mL). The resultant mixture was stirred at room temp. for 1 h, diluted with ethyl acetate, basified with aq. sodium bicarbonate. The organic extract was dried over magnesium sulfate, filtered, and concentrated under vacuum. The residue was subjected to column chromatography on silica gel eluting with 7% methanol in chloroform. Collection and concentration of appropriate fractions provided the title ketone.

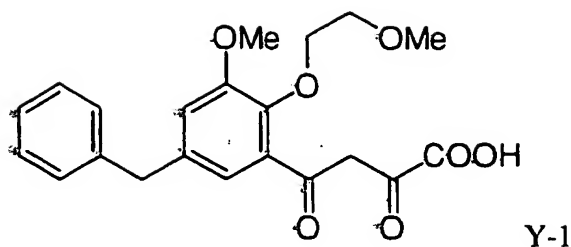
Step 6: 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)-phenyl]-2,4-dioxo-butyric acid W11



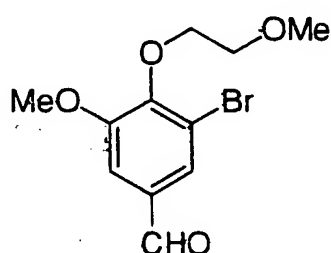
To a solution of 5-benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)-acetophenone (0.26 g) and diethyl oxalate (0.19 g) in THF (8 mL), sodium ethoxide (118 mg) was added. The resultant mixture was stirred at room temp. for 1 hr. under an atmosphere of argon. The resultant solution was treated with aq. NaOH (1M, 5 mL) and stirred at room temp for 1 hr. The product solution was neutralized with addition of aq. HCl, and concentrated under vacuum. The residue was dissolved in acetonitrile and acidified with aq TFA, and subjected to HPLC purification on reverse phase. Collection and lyophilization of appropriate fractions provided the title acid. ¹H NMR (CDCl₃) δ 7.67-7.11 (m, 8H), 4.26 (s, 2H), 3.97 (s, 2H), 3.74 (s, 3H), 2.86 (s, 6H).

EXAMPLE 31

4-(5-Benzyl-3-methoxy-2-methoxyethoxyphenyl)2,4-dioxobutyric acid

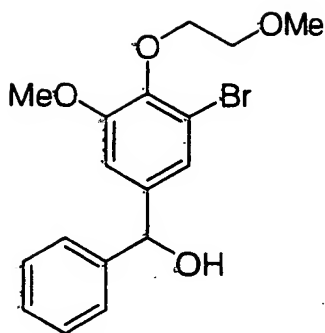


Step 1: 3-Bromo-4-(2-methoxyethoxy)-5-methoxybenzaldehyde



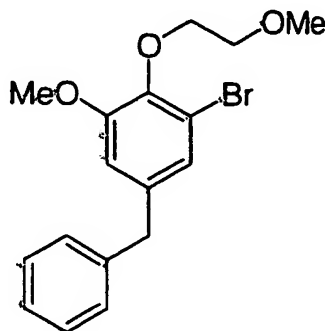
- 5 To a 500 mL round bottomed flask with a stirring bar, reflux condenser and an argon inlet was added 5-bromovanillin (10 g, 43.28 mmol), DMF (125 mL), powdered Cs₂CO₃ (28.2 g, 86.56 mmol) and 2-bromoethylmethyl ether (5.08 mL, 54.10 mmol). This well stirred mixture was heated at 75°C for 24h. The cooled mixture was filtered
- 10 through a frit to remove the cesium salts and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc and washed with water and brine. Drying (MgSO₄), filtration and removal of the solvent *in vacuo* gave an oil. ¹H NMR (CDCl₃): δ 3.44 (s, 3H); 3.77 (t, j=4 Hz, 2H); 3.92 (s, 3H); 4.27 (t, j=4 Hz, 2H); 7.38 (d, j=2 Hz, 1H); 7.65 (d, j=2Hz, 1H); 9.84 (s, 1H).
- 15

Step 2: 1-(3-Bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethanol.



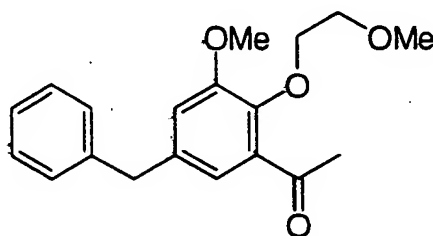
To a 1l round bottomed flask with a stirring bar and an argon inlet was added 3-bromo-4-(2-methoxyethoxy)-5-methoxybenzaldehyde (12.00g, 41.50 mmol) and dry THF (150 mL). This solution was cooled in an ice bath and phenylmagnesiumbromide in diethyl ether (16.6 mL of a 3.0M solution, 49.81 mmol) was added with a syringe. The resulting solution was stirred for 1h at 0°C. The reaction was quenched with aqueous NH₄Cl solution. The mixture was diluted with EtOAc and the layers were separated. The organic phase was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. This material was chromatographed on 400g of silica gel using 30/70 EtOAc-hexane as eluant. There was obtained 1-(3-bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethanol as an oil. ¹H NMR (CDCl₃): δ 2.29 (d, j=4Hz, 1H); 3.44 (s, 3H); 3.74 (t, j=4 Hz, 2H); 3.82 (s, 3H); 4.13 (t, j=4 Hz, 2H); 5.75 (d, j=4Hz, 1H); 6.88 (s, 1H); 7.12 (s, 1H); 7.35 (m, 5H).

Step 3: 1-(3-Bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethane.



To a 500 mL round bottomed flask with a stirring bar and a nitrogen inlet was added of 1-(3-bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethanol (12.83g, 34.94 mmol), dry methylene chloride (200 mL) and triethylsilane (13.87 mL, 87.34 mmol). This solution was cooled in an ice bath and borontrifluoride etherate (4.43 mL, 34.94 mmol) was added with a syringe over 5 min. The mixture was aged 2h at 0°C. The reaction was quenched with saturated aqueous sodium bicarbonate solution and the mixture was extracted with chloroform. The chloroform fraction was washed with brine, dried (MgSO₄), filtered and concentrated *in vacuo*. This material was chromatographed on 400g of silica gel using 20/80 EtOAc-hexane as eluant to give 9.45g of 1-(3-bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethane as an oil. ¹H NMR (CDCl₃): δ 3.44 (s, 3H); 3.74 (t, j=4 Hz, 2H); 3.77 (s, 3H); 3.88 (s, 2H); 4.13 (t, j=4 Hz, 2H); 6.64 (d, j=2Hz, 1H); 6.94 (d, j=2Hz, 1H); 7.26 (m, 5H).

Step 4: 1-(2-(2-Methoxyethoxy)-3-methoxy-5-phenylmethyl)-1-ethanone.

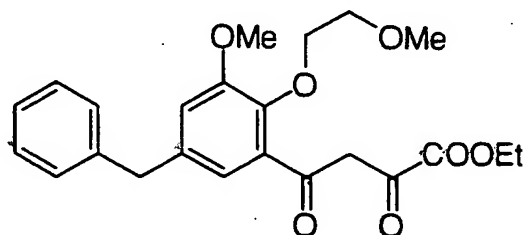


To a 25 mL glass pressure vessel with a stirring bar was added 1-(3-bromo-4-(2-methoxyethoxy)-5-methoxyphenyl)-1-phenylmethane (1.95g, 5.55 mmol) and 12 mL of DMF. This solution was degassed with a stream of nitrogen for 10 min. Palladium(II) acetate (0.25g, 1.11 mmol), DPPP (0.50g, 1.20 mmol), thallium(I) acetate (1.61g, 6.11 mmol), butylvinyl ether (3.62 mL, 27.75 mmol) and triethylamine (3.09 mL, 22.20 mmol) were added and the mixture was degassed for another 10 min. The vessel was sealed and heated at 100°C for 18h with vigorous stirring. The cooled mixture was filtered through a CELITE diatomaceous earth pad and the filtrate was concentrated *in vacuo*. The residue was dissolved in THF (30 mL) and 1N HCl (30 mL) was added. This solution

was stirred at ambient temperature 20h. The mixture was extracted with two portions of EtOAc. The combined EtOAc extracts were washed with water and brine. Drying (MgSO₄), filtration and removal of the solvent *in vacuo* gave a yellow oil. This material was chromatographed on 90g of silica gel using 30/70 EtOAc-hexane as eluant. There was obtained 1-(2-(2-methoxyethoxy)-3-methoxy-5-phenylmethyl)-1-ethanone as an oil. ¹H NMR (CDCl₃): δ 2.64 (s, 3H); 3.37 (s, 3H); 3.63 (t, j=4 Hz, 2H); 3.80 (s, 3H); 3.93 (s, 2H); 4.17 (t, j=4 Hz, 2H); 6.82 (d, j=2Hz, 1H); 7.04 (d, j=2Hz, 1H); 7.26 (m, 5H).

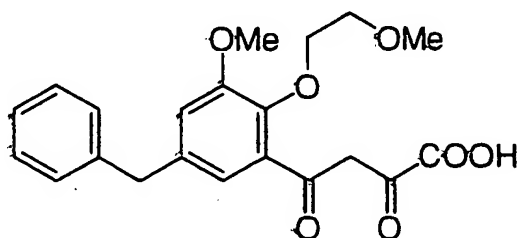
10

Step 5: Ethyl 4-(benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyrates.



To a 50 mL round bottomed flask with a stirring bar and a nitrogen inlet was added 1-(2-(2-methoxyethoxy)-3-methoxy-5-phenylmethyl)-1-ethanone (1.35g, 4.29 mmol), THF (30 mL), diethyl oxalate (1.75 mL, 12.88 mmol) and sodium ethoxide (0.41g, 6.00 mmol). This solution was stirred 2h at ambient temperature. The reaction was quenched with saturated aqueous NH₄Cl solution and extracted with EtOAc. The organic phase was washed with water and brine. Drying (MgSO₄), filtration and removal of the solvent *in vacuo* gave an oil. This material was exposed to high vacuum for 2 days to remove the excess diethyl oxalate giving 1.48g of ethyl 4-(benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyrates as an oil. ¹H NMR (CDCl₃): δ 1.38 (t, j=7Hz, 3H); 3.36 (s, 3H); 3.66 (t, j=4 Hz, 2H); 3.82 (s, 3H); 3.96 (s, 2H); 4.16 (t, j=4 Hz, 2H); 4.82 (q, j=7Hz, 2H); 6.87 (d, j=2Hz, 1H); 7.26 (m, 7H).

Step 6: 4-(Benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid.

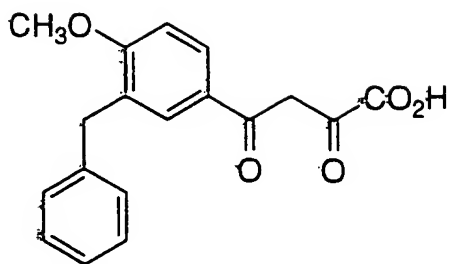


To a 200 mL round bottomed flask with a stirring bar and a nitrogen inlet was added ethyl 4-(benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyrate (1.48g, 3.57 mmol), THF (30 mL), methanol (30 mL), and sodium hydroxide solution (18 mL of a 1 N solution in water, 18 mmol). This mixture was stirred 2h at ambient temperature. The organic solvents were removed *in vacuo* and the aqueous residue was diluted with 30 mL of water. This solution was washed with ethyl ether (2 X 50 mL) then acidified with 1N HCl. This mixture was extracted with ethyl ether (100 mL). The ether solution was washed with water and brine. Drying (MgSO₄), filtration and removal of the solvent *in vacuo* gave a yellow oil. This material was crystallized by dissolving in 1:1 ether-hexane (~5mL) and storing in a freezer over night. The crystalline product was collected by filtration on a frit and dried *in vacuo* at ambient temperature to give 4-(benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid as yellow needles. MP: 83-85°C. Anal. Calc'd for C₂₁H₂₂O₇: C, 65.28; H, 5.74; Found: C, 65.28; H, 6.05. ¹H NMR (CDCl₃): δ 3.39 (s, 3H); 3.71 (t, j=4 Hz, 2H); 3.82 (s, 3H); 3.96 (s, 2H); 4.21 (t, j=4 Hz, 2H); 6.90 (d, j=2Hz, 1H); 7.28 (m, 6H); 9.60 (br s, 1H).

EXAMPLES 32-108

The following examples (32-108) may be prepared according to the general procedures outlined in the Schemes and in Examples 1 to 31.

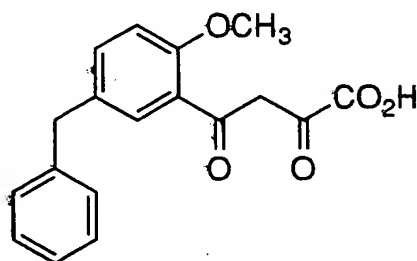
32. 4-(3-Benzyl-4-methoxyphenyl)-2,4-dioxobutyric acid



Anal. Calcd for $C_{18}H_{16}O_5$ 0.30 toluene: C, 71.01; H, 5.46.

Found: C, 71.05; H, 5.68.

5 33. 4-(5-Benzyl-2-methoxyphenyl)-2,4-dioxobutyric acid

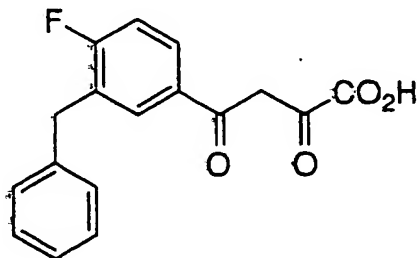


Anal. Calcd for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16.

Found: C, 68.89; H, 5.10.

10

34. 4-(3-Benzyl-4-fluorophenyl)-2,4-dioxobutyric acid



Anal. Calcd for $C_{17}H_{13}FO_4$ 0.15 H_2O : C, 67.38; H, 4.42.

15 Found: C, 67.31; H, 4.16.

35. 4-(3-Benzyl-4-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{19}H_{19}NO_4$ 1.42 TFA: C, 55.61; H, 4.41; N, 3.03.
Found: C, 55.51; H, 4.22; N, 2.95.

5 36. 4-[5-(2-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66.
Found: C, 67.42; H, 5.57.

10

37. 2,4-Dioxo-4-(3-pyridin-2-ylmethylphenyl)butyric acid

Anal. Calcd for $C_{16}H_{13}NO_4$ 0.7 TFA: C, 57.55; H, 3.80; N, 3.86.
15 Found: C, 57.73; H, 3.84; N, 3.79.

38. 4-(5-Benzyl-3-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid

20 Anal. Calcd for $C_{19}H_{19}NO_4$ 1.35 TFA: C, 57.40; H, 4.59; N, 3.19.
Found: C, 57.66; H, 4.87; N, 3.03.

39. 4-(5-Benzyl-3-methoxyphenyl)-2,4-dioxobutyric acid

25

Anal. Calcd for $C_{18}H_{16}O_5$ 0.15 H_2O : C, 68.62; H, 5.22.
Found: C, 68.59; H, 5.04.

30 40. 4-(5-Benzyl-2-benzyloxy-3-methoxyphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{25}H_{22}O_6 \cdot 0.30 H_2O$: C, 70.84; H, 5.37.

Found: C, 70.82; H, 5.22.

- 5 41. 4-[5-(3-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.41; H, 5.66.

Found: C, 67.33; H, 5.18.

10

42. 4-(5-Benzyl-3-benzyloxyphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{24}H_{20}O_5 \cdot 0.15 H_2O$: C, 73.69; H, 5.23.

- 15 Found: C, 73.65; H, 5.30.

43. 4-[5-Benzyl-2-(2-hydroxy)ethoxyphenyl]-2,4-dioxo-2-butanoic acid

- 20 Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30.

Found: C, 66.69; H, 5.51.

44. 2,4-Dioxo-4-(3-pyridin-3-ylmethylphenyl)butyric acid

25

Anal. Calcd for $C_{16}H_{13}NO_4 \cdot 1.1 TFA \cdot 0.35 MeCN$:

C, 53.65; H, 3.61; N, 4.47.

Found:

C, 53.56; H, 3.79; N, 4.47.

- 30 45. 4-[3-(3-Methyl-pyridin-2-ylmethyl)phenyl]-2,4-dioxo-butyric acid

Anal. Calcd for $C_{16}H_{13}NO_4$ 1 TFA: C, 55.48; H, 3.92; N, 3.41.

Found: C, 55.20; H, 4.01; N, 3.58.

5

46. 4-(5-Benzyl-2-methylsulfanylphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{18}H_{16}O_5$ 0.05 H_2O 0.20 HCl: C, 64.23; H, 4.88.

10 Found: C, 64.16; H, 4.76.

47. 4-(5-Benzyl-3-N-morpholinophenyl)-2,4-dioxobutyric acid

15 Anal. Calcd for $C_{21}H_{21}NO_5$ 1 TFA 0.2 H_2O : C, 56.95; H, 4.66; N, 2.89.

Found: C, 56.96; H, 5.18; N, 3.00.

48. 4-(8-Benzyl-4-methyl-3,4-dihydro-2h-benzo[1,4]oxazin-6-yl)-2,4-dioxobutyric acid

20

Anal. Calcd for $C_{20}H_{19}NO_5$ 0.15 MeCN 0.1 TFA:

C, 66.37; H, 5.31; N, 4.34.

Found: C, 66.41; H, 5.58; N, 4.41.

25

49. 4-[5-(2-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{19}H_{18}ClNO_4 \cdot 0.15$ hexane: C, 64.12; H, 5.44; N, 3.76.

Found: C, 64.02; H, 5.43; N, 3.56.

5 50. 4-[5-(3-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{19}H_{18}ClNO_4 \cdot 0.65$ Et₂O: C, 58.37; H, 5.78; N, 3.15.

Found: C, 58.12; H, 5.45; N, 2.77.

10

51. 4-(5-Benzyl-2,3,4-trimethoxyphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{20}H_{20}O_7 \cdot 0.15$ H₂O: C, 64.04; H, 5.46.

15 Found: C, 63.98; H, 5.29.

52. 4-(6-Benzylbenzo[1,3]dioxol-4-yl)-2,4-dioxobutyric acid

20 Anal. Calcd for $C_{18}H_{14}O_6 \cdot 0.3$ H₂O $\cdot 0.1$ Et₂O: C, 65.16; H, 4.64.

Found: C, 65.25; H, 4.65.

53. 4-[3-Benzyl-5-(morpholine-4-carbonyl)phenyl]-2,4-dioxobutyric acid

25

Anal. Calcd for $C_{22}H_{21}NO_6 \cdot 0.25$ CHCl₃ $\cdot 0.15$ hexane:

C, 63.45; H, 5.37; N, 3.20.

Found: C, 63.42; H, 5.30; N, 3.20.

30 54. 4-(3-Benzyl-5-pyridine-2-ylmethylphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{23}H_{19}NO_4$ 1.0 TFA 0.2 hexane:

C, 62.39; H, 4.19; N, 2.46.

Found:

C, 62.35; H, 4.55; N, 2.78.

5

55. 4-[3-Benzyl-5-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{22}H_{23}NO_5$:

C, 58.18; H, 4.88; N, 2.83.

10 Found:

C, 58.26; H, 4.76; N, 2.77.

56. 4-(3-Benzyl-5-pyridine-3-ylmethylphenyl)-2,4-dioxobutyric acid

15 Anal. Calcd for $C_{23}H_{19}NO_4$ 1.0 TFA:

C, 61.60; H, 4.14; N, 2.87.

Found:

C, 61.65; H, 4.43; N, 2.92.

57. 4-[3-Benzyl-5-(2-dimethylamino-1-hydroxy-1-methylethyl)phenyl]-2,4-dioxobutyric acid

20

Anal. Calcd for $C_{22}H_{25}NO_5$ 1.20 H_2O :

C, 55.53; H, 5.51; N, 2.70.

Found:

C, 55.55; H, 5.23; N, 2.55.

25 58. 4-(5-Benzyl-2-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{19}H_{19}NO_4$ 1.0 TFA 0.55 H_2O : C, 56.13; H, 4.73; N, 3.12.

Found:

C, 56.11; H, 4.67; N, 3.11.

30

59. 4-(5-Benzyl-2-fluorophenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{17}H_{13}FO_4 \cdot 0.05 H_2O \cdot 0.05 Et_2O$: C, 67.75; H, 4.50.

5 Found: C, 67.83; H, 4.46.

60. 4-(5-Benzyl-3-hydroxymethyl-2-methoxyphenyl)-2,4-dioxobutyric acid

10 Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30.

Found: C, 66.91; H, 5.39.

61. 4-[5-Benzyl-2-(pyrazin-2-yloxy)phenyl]-2,4-dioxobutyric acid

15

Anal. Calcd for $C_{21}H_{16}N_2O_5 \cdot 0.45 TFA \cdot 1.15 H_2O$:

C, 58.66; H, 4.21; N, 6.25.

Found: C, 58.67; H, 4.15; N, 6.55.

20 62. 4-[3-Benzyl-5-(2-oxopiperidin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{23}H_{23}NO_5$: C, 70.22; H, 5.89; N, 3.56.

25 Found: C, 69.86; H, 5.55; N, 3.40.

63. 4-[5-Benzyl-2-methoxy-3-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid

30

Anal. Calcd for $C_{23}H_{25}NO_6$: C, 57.14; H, 4.99; N, 2.67.

Found: C, 57.57; H, 5.34; N, 2.47.

5 64. 4-[3-(2-Chlorobenzyl)-5-pyridin-2-ylmethylphenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{23}H_{18}ClNO_4 \cdot 1.0 H_2O$: C, 64.86; H, 4.73; N, 3.29.

Found: C, 64.89; H, 4.37; N, 2.97.

10

65. 4-[5-Benzyl-2-methoxy-3-(4-methylpiperazin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid

15 Anal. Calcd for $C_{24}H_{28}N_2O_5 \cdot 2.2 TFA$: C, 51.01; H, 4.57; N, 4.22.

Found: C, 51.03; H, 4.52; N, 4.12.

66. 4-(5-Benzyl-2-methoxymethylphenyl)-2,4-dioxobutyric acid

20

Anal. Calcd for $C_{19}H_{18}O_5 \cdot 0.10$ hexane: C, 70.27; H, 5.84.

Found: C, 70.40; H, 5.48.

25 67. 4-[3-(2-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{22}H_{22}NO_5F \cdot 2.25 TFA \cdot 0.15 H_2O$:

C, 48.32; H, 3.76; N, 2.13.

30 Found:

C, 48.30; H, 3.77; N, 1.82.

68. 4-[3-(4-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid

5

Anal. Calcd for $C_{22}H_{22}NO_5F$ 1.05 TFA 0.15 H_2O :

C, 55.46; H, 4.51; N, 2.68.

Found:

C, 55.48; H, 4.53; N, 2.43.

10 69. 4-[3-(3-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{22}H_{22}NO_5F$ 1.45 TFA 0.50 H_2O :

C, 52.12; H, 4.30; N, 2.44.

15 Found:

C, 52.11; H, 4.29; N, 2.24.

70. 4-[5-Benzyl-2-methoxy-3-(tert-butylcarbonyl)phenyl]-2,4-dioxobutyric acid

20

Anal. Calcd for $C_{23}H_{25}NO_7$ 0.25 EtOAc 0.05 Et_2O :

C, 64.13; H, 6.12; N, 3.09.

Found:

C, 64.13; H, 6.10; N, 3.13.

25 71. 4-(3-Benzyl-5-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{20}H_{17}N_3O_4$ 0.1 hexane: C, 66.51; H, 4.99; N, 11.30.

Found:

C, 66.87; H, 4.87; N, 11.65.

30

72. 4-[5-Benzyl-3-(N'-methyl-N-piperazinyl)phenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{22}H_{24}N_3O_4$: C, 63.38; H, 6.04; N, 6.72.

5 Found: C, 63.34; H, 6.12; N, 6.56.

73. 4-(3-Benzyl-5-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid

10 Anal. Calcd for $C_{20}H_{17}N_3O_4$: C, 66.11; H, 4.72; N, 11.56.

Found: C, 66.26; H, 4.99; N, 11.59.

74. 4-(6-Benzyl-3-oxo-3,4-dihydro-2-H-benzo[1,4]oxazin-8-yl)-2,4-dioxobutyric acid

15

Anal. Calcd for $C_{19}H_{15}NO_6 \cdot 0.30 H_2O$: C, 63.61; H, 4.38; N, 3.90.

Found: C, 63.69; H, 4.51; N, 3.89.

20 75. 4-[5-Benzyl-2-(pyrimidin-2-yloxy)phenyl]-2,4-dioxobutyric acid

Anal. Calcd for $C_{21}H_{16}N_2O_5 \cdot 0.40 H_2O \cdot 0.45 TFA$:

C, 60.48; H, 4.00; N, 6.44.

25 Found: C, 60.51; H, 3.96; N, 6.31.

76. 4-(5-Benzyl-3-amino-2-methoxyphenyl)-2,4-dioxobutyric acid

FAB MS M+1 = 345

77. 4-(5-Benzyl-2-ethoxyphenyl)-2,4-dioxobutyric acid

5

Anal. Calcd for C₁₈H₁₆O₅ 0.15 hexane: C, 70.44; H, 5.97.

Found: C, 70.62; H, 5.62.

10

78. 4-[5-Benzyl-2-(2-morpholin-4-yl-ethoxy)phenyl]-2,4-dioxobutyric acid

Anal. Calcd for C₂₃H₂₅NO₆ 0.65 CH₂Cl₂ 0.10 Et₂O:

C, 60.93; H, 5.80; N, 2.95.

Found: C, 61.11; H, 5.78; N, 2.75.

15

79. 4-(5-Benzyl-2-trifluoroethoxyphenyl)-2,4-dioxobutyric acid

Anal. Calcd for C₁₉H₁₅F₃O₅ 0.05 Et₂O: C, 60.05; H, 4.07.

20 Found: C, 60.00; H, 4.08.

80. 4-(5-Benzyl-2-cyclobutyloxyphenyl)-2,4-dioxobutyric acid

25 Anal. Calcd for C₂₁H₂₀O₅ 0.05 H₂O 0.15 Et₂O: C, 71.19; H, 5.97.

Found: C, 71.20; H, 5.99.

81. 4-(5-Benzyl-2-cyclopentyloxyphenyl)-2,4-dioxobutyric acid

30

Anal. Calcd for $C_{22}H_{22}O_5$ 0.20 toluene 0.15 Et_2O : C, 72.80; H, 6.39.

Found: C, 72.81; H, 6.40.

5 82. 4-(3-Benzyl-5-tetrazol-2-ylmethylphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{19}H_{16}N_4O_4$: C, 61.99; H, 4.59; N, 14.91.

Found: C, 62.00; H, 4.74; N, 14.88.

10 83. 4-(5-Benzyl-2,3-diisopropoxyphenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{23}H_{26}O_6$ 0.2 hexane: C, 69.92; H, 6.98.

Found: C, 69.86; H, 6.99.

15

84. 4-(5-Benzyl-2-isopropoxy-3-N-methylaminophenyl)-2,4-dioxobutyric acid

20 Anal. Calcd for $C_{21}H_{23}NO_5$ 0.10 TFA 0.90 H_2O :

C, 55.28; H, 5.20; N, 2.80.

Found: C, 55.26; H, 5.12; N, 2.82.

25 85. 4-(5-Benzyl-2-isopropoxy-3-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid

Anal. Calcd for $C_{22}H_{25}NO_5$ 0.10 TFA: C, 57.95; H, 5.27; N, 2.82.

Found: C, 58.09; H, 5.10; N, 2.83.

30

86. 4-[5-Benzyl-2-isopropoxy-3-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-dioxobutyric acid

5 Anal. Calcd for $C_{24}H_{29}NO_6$ 1.70 TFA 0.05 H_2O :

C, 52.89; H, 4.99; N, 2.25.

Found:

C, 52.92; H, 5.02; N, 2.01.

87. 4-[5-Benzyl-2-isopropoxy-3-(morpholinomethyl)phenyl]-2,4-dioxo-
10 butyric acid

Anal. Calcd for $C_{25}H_{29}NO_6$ 1.0 HCl:

C, 63.09; H, 6.35; N, 2.94.

Found:

C, 63.43; H, 6.46; N, 2.65.

15

88. 4-(5-Benzyl-2-isopropoxy-3-N,N-dimethylaminomethylphenyl)-2,4-dioxo-butylric acid

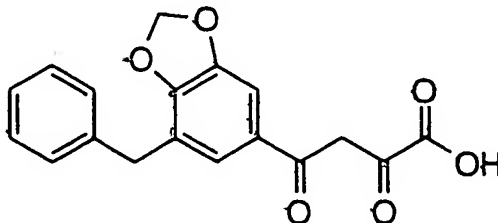
20 Anal. Calcd for $C_{23}H_{27}NO_5$ 0.10 TFA:

C, 58.70; H, 5.52; N, 2.74.

Found:

C, 58.42; H, 5.27; N, 2.45.

89. 4-(7-Benzylbenzo[1,3]dioxol-5-yl)-2-hydroxy-4-oxobut-2-enoic acid



25

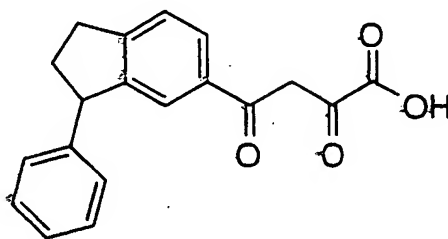
Anal calc for $C_{18}H_{14}O_6$.1 ethyl acetate

C, 65.94 ; H, 4.45

Found

C, 65.95 ; H, 4.84

90. 2-Hydroxy-4-oxo-4-(3-phenylindan-5-yl)but-2-enoic acid



5

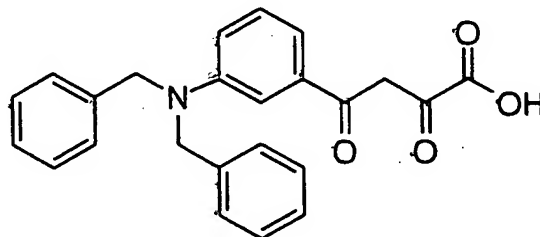
Anal calc for $C_{19}H_{16}O_4 \cdot 0.05 H_2O$

C, 73.79 ; H, 5.25

Found

C, 73.48 ; H, 5.33

10 91. 4-(Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid

Anal calc for $C_{24}H_{21}NO_4 \cdot 0.1$ ethyl acetate

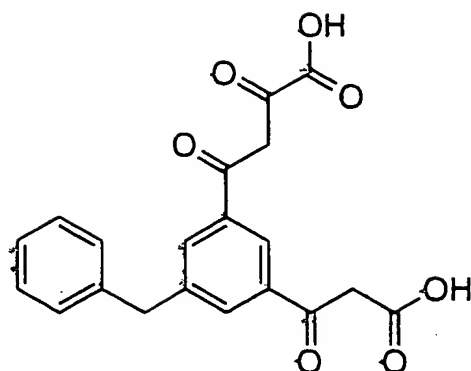
C, 73.95 ; H, 5.55 ; N, 3.54

Found

C, 73.69 ; H, 5.90 ; N, 3.22

15

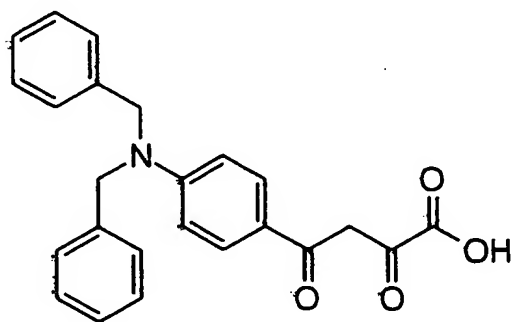
92. 3-(3-Benzyl-5-carboxyacetylphenyl)-3-oxopropionic acid



Anal calc for $C_{19}H_{16}O_6 \cdot 1.5 H_2O$ C, 62.12 ; H, 5.21

Found C, 61.98 ; H, 5.28

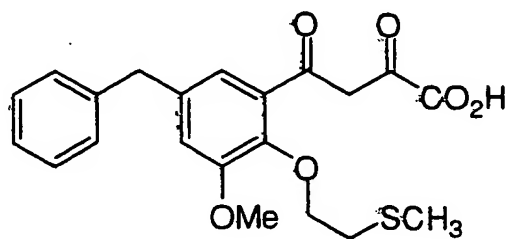
5 93. 4-(4-Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid



Anal calc for $C_{24}H_{21}NO_4 \cdot 0.05$ ethyl acetate C, 74.17 ; H, 5.51 ; N, 3.57

Found C, 74.05 ; H, 5.38 ; N, 3.29

10 94. 4-(5-Benzyl-3-methoxy-2-methylthioethoxyphenyl)-2,4-dioxobutyric acid

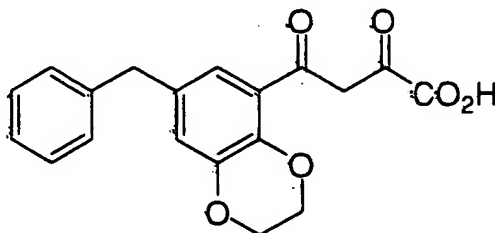


Anal. Calc'd for $C_{21}H_{22}O_6S$: C, 62.67; H, 5.51

Found: C, 62.26; H, 5.65

mp: 99-100°C

- 5 95. 4-(7-Benzyl-2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,4-dioxobutyric acid



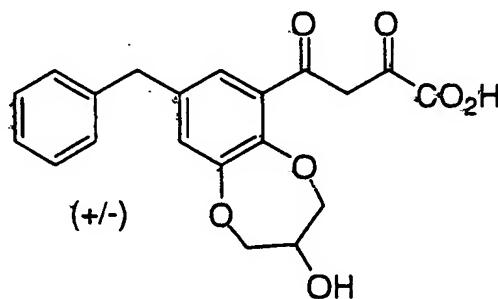
Anal. Calc'd for $C_{19}H_{16}O_6$: C, 67.05; H, 4.74

Found: C, 66.35; H, 4.87

mp: 154-155°C

10

96. (+/-) 4-(8-Benzyl-3-hydroxy-3,4-dihydro-2H-benzo[B][1,4]di-oxepin-6-yl)-2,4-dioxobutyric acid



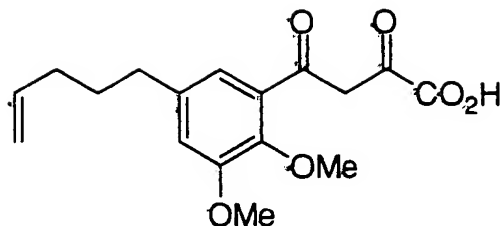
Anal. Calc'd for $C_{20}H_{18}O_7$: C, 64.06; H, 4.90

Found: C, 64.06; H, 5.14

15

mp: 182-183°C

97. 4-(2,3-Dimethoxy-5-pent-4-enylphenyl)-2,4-dioxobutyric acid



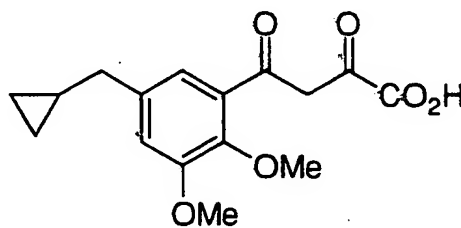
Anal. Calc'd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29

Found: C, 64.05; H, 6.05

mp: 75-76°C

5

98. 4-(5-Cyclopropylmethyl-2,3-dimethoxyphenyl)-2,4-dioxobutanoic acid



Anal. Calc'd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92

Found: C, 62.75; H, 5.79

10

mp: 101-103°C

15

99. 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutanoic acid

1H NMR ($CDCl_3$) δ 7.75 (s, 1H), 7.59 (s, 1H), 7.31-7.12 (m, 7H), 5.63 (s, 2H), 4.19 (m, 1H), 3.92 (s, 2H), 1.29 (d, $J = 6$ Hz, 6H).

20

100. 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutanoic acid

¹H NMR (CDCl₃) δ 8.42 (s, 1H), 8.02 (s, 1H), 7.58 (s, 1H), 7.34-7.14 (m, 7H), 5.37 (s, 2H), 4.23 (m, 1H), 3.95 (s, 2H), 1.31 (d, J = 6 Hz, 6H).

101. 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-
5 dioxobutyric acid

Anal. Calcd for C₂₃H₂₇NO₆ 0.40 HCl 0.25 Et₂O:

10 Found: C, 64.54; H, 6.75; N, 3.14.
C, 64.42; H, 6.76; N, 3.11.

102. 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid

15 Anal. Calcd for C₁₇H₁₂F₂O₄: C, 64.15; H, 3.80.
Found: C, 64.29; H, 3.73.

103. 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid

20

Anal. Calcd for C₂₀H₁₈O₅ 0.2 hexane: C, 71.60; H, 5.90.
Found: C, 71.78; H, 5.55

104. 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-
25 butyric acid TFA salt

Anal. Calcd for C₂₆H₃₁NO₅ 1.15 TFA: C, 59.77; H, 5.70; N, 2.46.
Found: C, 59.68; H, 5.70; N, 2.33.

30

105. 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyrlic acid

5 Anal. Calcd for $C_{22}H_{25}NO_5$ 0.80 H_2O 0.20 EtOAc:

C, 65.91; H, 6.84; N, 3.37.

Found:

C, 65.91; H, 6.91; N, 3.41.

106. 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyrlic
10 acid

Anal. Calcd for $C_{23}H_{25}NO_5$ 1.7 H_2O 0.30 EtOAc:

C, 64.23; H, 6.86; N, 3.10.

15 Found:

C, 64.23; H, 6.62; N, 3.08.

107. 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyrlic acid

20 Anal. Calcd for $C_{28}H_{29}N_2O_4$ 0.5 HCl:

C, 70.83; H, 6.00; N, 5.62.

Found:

C, 70.73; H, 6.00; N, 5.62.

108. 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-
25 dioxo-butyrlic acid

Anal. Calcd for $C_{26}H_{26}N_2O_5$ 1.25 H_2O 0.15 methyl t-butyl ether:

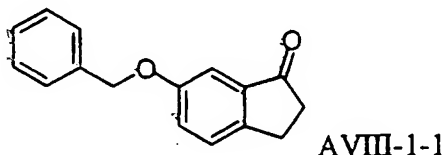
C, 66.62; H, 6.33; N, 5.81.

30 Found:

C, 66.58; H, 6.09; N, 5.43.

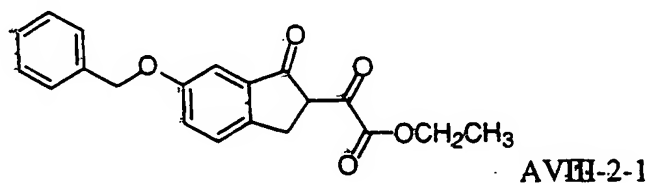
EXAMPLE 109

(6-Benzyloxy-1-oxo-indan-2-ylidene)-hydroxyacetic acid AVIII-3-1

Step 1: 6-Benzyloxvindan-1-one AVIII-1-1

- 5 To a solution of 6-hydroxy-indan-1-one (*J. Chem. Soc. Perkin Trans. 1*, 1984, 4, 687-695) (29g, 196 mmole) in DMF (250 mL), was added under a N₂ atmosphere at ambient temperature K₂CO₃ (69.1g, 500 mmole) and benzyl bromide (27.7 mL, 250 mmole). The reaction was set to reflux for 4 hours. The mixture was allowed to cool to room temperature, poured
10 into water, extracted with CH₂Cl₂, the organic layer was separated and dried with MgSO₄, the solvent evaporated and the product purified by chromatography over silica to obtain AVIII-1-1 as a yellowish solid. ¹H NMR (400 MHz, CDCl₃) δ 7.45-7.3 (m, 6H), 7.24 (m, 2H), 5.17 (s, 2H), 3.05 (m, 2H), 2.7 (m, 2H). mass spec EI: m/z (relative abundance) 238 (M⁺),
15 91 (100).

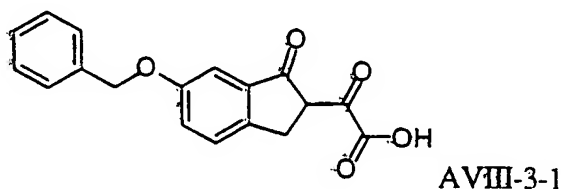
Step 2: (6-Benzyloxy-1-oxo-indan-2-ylidene)-hydroxyacetic acid ethyl ester AVIII-2-1



- 20 To a solution of AVIII-1-1 (1.9, 8 mmole) and diethyl oxalate (Aldrich, 2.17 mL, 16 mmole) in THF (8 mL) was added in portions NaOEt (Aldrich, 1.088g, 16 mmole). The reaction was stirred at ambient temperature under a N₂ atmosphere for 1.5 hours. The reaction was diluted with CH₂Cl₂, quenched with saturated NaHCO₃ (aq), the organic
25 layer was separated and dried with MgSO₄, the mixture was filtered, the solvent evaporated and the crude purified by preparative silica HPLC

eluting with 10:30:60 EtOAc / CH₂Cl₂ / Hexanes to afford the product as a yellow solid. melting point 118-119°C (uncorrected). ¹H NMR (400 MHz, CDCl₃) δ 7.48-7.30 (m, 8H), 5.12 (s, 2H), 4.41 (q, J=7.24 Hz, 2H), 3.91 (s, 2H), 1.43 (t, J=7.24 Hz, 3H). mass spec EI: m/z (relative abundance) 338 (M⁺), 91 (100).

Step 3: (6-Benzyloxy-1-oxo-indan-2-ylidene)-hydroxyacetic acid
AVIII-3-1

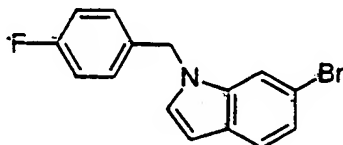


- 10 A solution of AVIII-2-1 (500mg, 1.47 mmole) in 1,4-dioxane (3 mL) and 3N HCl (3 mL) was heated in a sealed tube at 70°C overnight. The reaction was then allowed to cool to ambient temperature and poured into 1N HCl (25 mL), the solid was filtered, dried under vacuum and the product purified by trituration with Et₂O / hexanes to afford AVIII-3-1
- 15 as a yellow solid. melting point 188-189°C (uncorrected). ¹H NMR (400 MHz, DMSO) δ 7.56 (d, J=8.4, 1H), 7.47 (m, 2H), 7.42-7.33 (m, 5H), 5.21 (s, 2H), 3.77 (s, 2H). mass spec (FAB, m+1) 311

EXAMPLE 110

- 20 1-[1-(4-Fluorobenzyl)-6-indolyl]-2,4-dioxobutanoic acid AVII-3-1

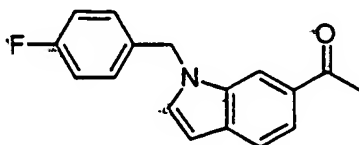
Step 1: 6-Bromo-1-(4-fluorobenzyl)indole



A solution of 6-bromoindole (J. Org. Chem. 1986, 51, 5106) (3.00 g, 15.3 mmol) in DMF (65 mL) was treated with NaH (734 mg of a 60% suspension in mineral oil, 18.4 mmol). After 30 min, 4-fluorobenzyl bromide (1.90 mL, 15.3 mmol) was added. When starting material was consumed, the reaction mixture was poured into 1N HCl and extracted with EtOAc (3x), the combined organic layers were dried (MgSO₄) and concentrated. Chromatography of the residue (4:1/hexanes:EtOAc) provided the product.

¹H NMR (400 MHz, CDCl₃) δ 7.49 (d, J = 8.4 Hz, 1H), 7.41 (s, 1H), 7.21 (dd, J = 8.4, 1.0 Hz, 1H), 7.08-7.04 (m, 3H), 7.15-6.96 (m, 2H), 6.52 (d, J = 3.2 Hz, 1H), 5.24 (s, 2H). mass spec (EI, M⁺) 303, 305

Step 2: 1-[1-(4-Fluorobenzyl)-6-indolyl]-ethanone AVII-1-1

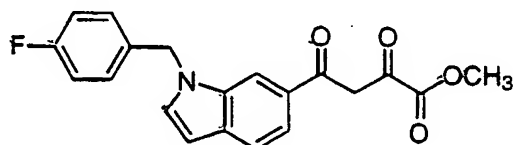


AVII-1-1

To a solution of 6-bromo-1-(4-fluorobenzyl)indole (2.50 g, 8.20 mmol) in THF (40 mL) at -78 °C was added t-butyllithium (10.6 mL of a 1.7 M solution in pentane, 18.0 mmol) dropwise. After stirring at -78 °C for 30 min, N-methoxy-N-methylacetamide (1.20 g, 12.3 mmol) was added and the mixture was stirred at -78 °C for 2 h and rt for 1 h before adding sat. NH₄Cl (5 mL). The reaction mixture was poured onto water and extracted with EtOAc (3x). The combined organic extracts were washed with sat. NaCl and dried (MgSO₄). Concentration followed by chromatography of the residue (4:1/hexanes:EtOAc) provided 750 mg (34%) of product.

^1H NMR (400 MHz, CDCl_3) δ 8.00 (s, 1H), 7.74 (dd, J = 8.3, 1.5 Hz, 1H), 7.67 (d, J = 8.3 Hz, 1H), 7.28 (d, J = 3.1 Hz, 1H), 7.12-7.07 (m, 2H), 7.00 (m, 2H), 6.60 (d, J = 3.1 Hz, 1H), 5.38 (s, 2H), 2.63 (s, 3H).

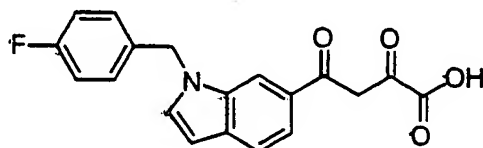
5 Step 3: 1-[1-(4-Fluorobenzyl)-6-indolyl]-2,4-dioxobutanoic acid
 methyl ester AVII-2-1



AVII-2-1

To a solution of AII-1-1 (700 mg, 2.60 mmol) in THF (10 mL) was added dimethyl oxalate (460 mg, 3.90 mmol) followed by NaH (156 mg of a 60%
10 suspension in mineral oil, 3.90 mmol). Methanol (2 drops) was added and the reaction mixture was heated to reflux. After 1 h, 1 N HCl (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic extracts were washed with sat. NaCl (20 mL) and dried (MgSO_4). Concentration followed by medium-pressure liquid
15 chromatography on silica gel, eluting with 5:5:1/
 CH_2Cl_2 :hexanes:EtOAc, afforded 597 mg (65%) of product. ^1H NMR (400 MHz, CDCl_3) δ 8.05 (s, 1H), 7.76 (dt, J = 8.4, 1.1 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.31 (dd, J = 3.1, 1.1 Hz, 1H), 7.14 (s, 1H), 7.11 (dd, J = 8.4, 5.2 Hz, 2H), 7.01 (t, J = 8.4 Hz, 2H), 6.62 (d, J = 3.2 Hz, 1H), 5.38 (s, 2H), 3.95 (s,
20 3H).

Step 4: 1-[1-(4-Fluorobenzyl)-6-indolyl]-2,4-dioxobutanoic acid AVII-
3-1



AVII-3-1

25 To a solution of AVII-2-1 (597 mg, 1.69 mmol) in THF (10 mL) was added 1 N NaOH (5 mL). After stirring for 14 h at rt, the mixture was poured into 1 N NaOH (20 mL) and extracted with Et_2O (3 x 20 mL). The Et_2O

extracts were discarded. The aqueous phase was treated with 3 N HCl (30 mL), extracted with CH₂Cl₂ (3 x 20 mL) and the combined organic extracts dried (MgSO₄). Concentration provided a bright red solid which was triturated with Et₂O to provide the product. mp 173-174 °C

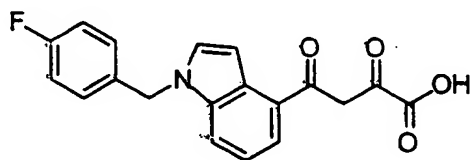
5 (uncorrected). ¹H NMR (400 MHz, *d*₆-DMSO) δ 8.37 (s, 1H), 7.79 (d, *J* = 3.0 Hz, 1H), 7.75 (dt, *J* = 8.4, 1.3 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.28 (dd, *J* = 8.7, 5.6 Hz, 2H), 7.25 (s, 1H), 7.15 (t, *J* = 8.2 Hz, 2H), 6.63 (d, *J* = 3.0 Hz, 1H), 5.62 (s, 2H). mass spec (negative mode electrospray, M-H) 338

10

EXAMPLE 111

1-[1-(4-Fluorobenzyl)-4-indolyl]-2,4-dioxobutanoic acid AVII-3-2

Compound AVII-3-2 was prepared in a manner similar to that described for AVII-3-1 by replacing 6-bromoindole with 4-bromoindole (J. Org. Chem. 1986, 51, 5106).



15

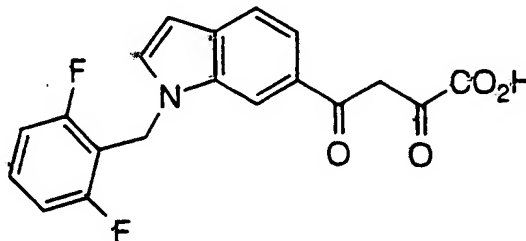
AVII-3-2

mp 156-157 °C (uncorrected). ¹H NMR (400 MHz, *d*₆-DMSO) δ 7.88 (d, *J* = 8.3 Hz, 1H), 7.85 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 3.0 Hz, 1H), 7.30-7.25 (m, 1H), 7.17-7.11 (m, 4H), 5.52 (s, 2H). mass spec (negative mode electrospray, M-H) 338

20

EXAMPLE 112

4-[1-(2,6-Difluorobenzyl)-1*H*-indol-6-yl]-2,4-dioxobutyric acid



25 ES MS Exact Mass Calcd. for C₁₉H₁₃F₂NO₄+H 358.0885

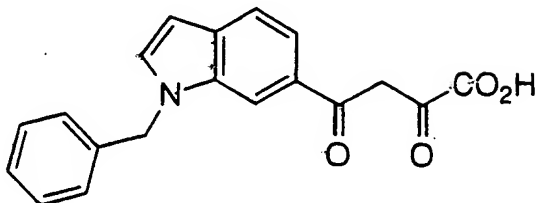
Found

358.0887

EXAMPLE 113

4-(1-Benzyl-1H-indol-6-yl)-2,4-dioxobutyric acid

5

Anal. Calcd for $C_{19}H_{15}NO_4 \cdot 0.75 HCl \cdot 0.05 H_2O$:

C, 65.27; H, 4.57; N, 4.01.

Found:

C, 65.26; H, 4.25; N, 3.87.

10

EXAMPLE 114

4-(5-Benzyl-2-methoxypyridin-3-yl)-2,4-dioxobutyric acid

15 Anal. Calcd for $C_{17}H_{15}NO_5 \cdot 0.05 Et_2O \cdot 0.05 H_2O$:

C, 64.98; H, 4.95; N, 4.41.

Found:

C, 64.91; H, 4.89; N, 4.15.

EXAMPLE 115

20 The Compounds in the following Table were made according to the procedures outlined in the Schemes and in Examples 1 to 31.

<u>COMPOUND NAME</u>	<u>EXACT MASS CALC (m/z):</u>	<u>FOUND (m/z):</u>
4-[3-(2,4-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid	319.0776	319.0781
2,4-dioxo-4-[3-(2,6-difluoro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 336.1042	336.1063
2,4-dioxo-4-[3-(2,4,6-trifluoro-benzyl)-phenyl]-butyric acid (sodium salt)	NH ₄ ⁺ 354.0948	354.0955
2,4-dioxo-4-[3-(2-fluoro-3-chloro-benzyl)-phenyl]-butyric acid	C ₁₇ H ₁₂ ClFO ₄ NH ₄ ⁺ 352.0746	352.0763
2,4-dioxo-4-[3-(2-methyl-4-fluoro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 332.1293	332.1307

4-[3-(2,3-dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid	C ₁₇ H ₁₂ Cl ₂ O ₄ .NH ₄ ⁺ 368.0451	368.0443
4-[3-(2-chloro-3-methylbenzyl)phenyl]-2,4-dioxobutyric acid	C ₁₈ H ₁₅ ClO ₄ .NH ₄ ⁺ 348.0997	348.1015
2,4-dioxo-4-[3-(2,6-dichloro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 368.0451	368.046
2,4-dioxo-4-[3-(2,3,4,5,6-penta-fluoro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 390.0759	390.0775
4-[3-(2-fluorobenzyl)phenyl]-2,4-dioxobutyric acid	C ₁₇ H ₁₃ FO ₄ .NH ₄ 318.1136	318.1133
2,4-dioxo-4-[3-(2-chloro-4-fluoro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 352.0746	352.0752

4-[3-(2-methylbenzyl)phenyl]-2,4-dioxobutyric acid	$C_{18}H_{16}O_4.NH_4+$ 314.1387	314.1395
2,4-dioxo-4-[3-(2-methoxybenzyl)phenyl]butyric acid	NH_4+ 330.1336	330.135
4-[3-(2-chlorobenzyl)phenyl]-2,4-dioxobutyric acid	$C_{17}H_{13}ClO_4.NH_4+$ 334.0841	334.0854
4-[3-(2-bromobenzyl)phenyl]-2,4-dioxobutyric acid	$C_{17}H_{13}BrO_4.NH_4+$ 378.0335	378.034
4-[5-(4-fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-butyric acid	361.1082	361.109
4-[3-(3-chloro-2-methylbenzyl)phenyl]-2,4-dioxobutyric acid	$C_{18}H_{15}ClO_4.NH_4+$ 348.0997	348.1013

4-[3-(2,3-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid	C ₁₇ H ₁₂ F ₂ O ₄ .NH ₄ ⁺ 336.1042	336.1044
4-(3,5-dibenzylphenyl)-2,4-dioxo-butyric acid	C ₂₄ H ₂₀ O ₄ .NH ₄ ⁺ 390.1700	390.171
2,4-dioxo-4-[3-(2-trifluoromethylbenzyl)phenyl]butyric acid	NH ₄ ⁺ 368.1104	368.1111
4-[3-(4-fluorobenzyl)phenyl]-2,4-dioxobutyric acid	C ₁₇ H ₁₃ FO ₄ 301.0876	301.0885
4-[3-(3-chlorobenzyl)phenyl]-2,4-dioxobutyric acid	C ₁₇ H ₁₃ ClO ₄ .NH ₄ ⁺ 334.0841	334.0847
2,4-dioxo-4-[3-(2-bromo-3-chloro-benzyl)-phenyl]-butyric acid	NH ₄ ⁺ 411.9946	411.9944

4-(3-benzylphenyl)-2,4-dioxo-butyric acid	$C_{17}H_{14}O_4.NH_4+$ 300.123	300.124
4-[3-(2-fluoro-3-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid sodium salt	315.1027	315.1034
4-[3-(3-chloro-4-fluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid	$C_{17}H_{12}ClFO_4.NH_4$ + 352.0746	352.0733
2,4-dioxo-4-[3-(2-bromo-4-fluoro-benzyl)-phenyl]-butyric acid	NH_4+ 396.0241	396.0247
4-[3-(3-bromobenzyl)phenyl]-2,4-dioxobutyric acid	$C_{17}H_{13}BrO_4$ 361.0075	361.0101
4-[3-(2,5-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid	$C_{17}H_{12}F_2O_4.NH_4+$ 336.1042	336.1046

4-[3-(5-chloro-2-fluoro-benzyl)phenyl]-2,4-dioxobutyric acid	$C_{17}H_{12}ClFO_4.NH_4$ + 352.0746	352.0753
4-[3-(3-methylbenzyl)phenyl]-2,4-dioxobutyric acid	$C_{18}H_{16}O_4$ 297.1121	297.112
4-(3-benzyl-4-methyl-phenyl)-2,4-dioxo-butyric acid	297.1121	297.1142
4-[3-(3,4-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid	319.0776	319.078
4-[3-(2,5-dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid	$C_{17}H_{12}Cl_2O_4.NH_4+$ 368.0451	368.0465
4-[3-(2-chloro-6-methyl-benzyl)phenyl]-2,4-dioxobutyric acid	$C_{18}H_{15}ClO_4.NH_4+$ 348.0997	348.1012

2,4-dioxo-4-[3-(2-trifluoromethyl-4-chlorobenzyl)-phenyl]-butyric acid	NH ₄ ⁺ 386.1010	386.1009
4-[3-(2-bromo-5-chlorobenzyl)-phenyl]-2,4-dioxo-butylric acid	C ₁₇ H ₁₂ BrClO ₄ .NH ₄ + 411.9947	411.9966
4-(3-naphthalen-1-ylmethyl-phenyl)-2,4-dioxo-butylric acid	333.1121	333.1121
2,4-dioxo-4-[3-(3-fluorobenzyl)phenyl]butylric acid	NH ₄ ⁺ 318.1136	318.114
2,4-dioxo-4-(3-phenylsulfanyl-phenyl)-butylric acid	301.0535	301.0524
2,4-dioxo-4-[3-(1-phenylethyl)phenyl]butylric acid	NH ₄ ⁺ 314.1387	314.1401

4-(3-benzyl-4,5-dimethylphenyl)-2,4-dioxo-butyrlic acid	311.1278	311.1293
2,4-dioxo-4-[3-(3-methoxybenzyl)phenyl]butyric acid	NH ₄ ⁺ 330.1336	330.1341
4-[3-(5-methyl-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyrlic acid	NH ₄ ⁺ 320.0951	320.0967
4-[3-(5-chloro-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyrlic acid	NH ₄ ⁺ 340.0405	340.0418
4-(3-benzyl-5-methylphenyl)-2,4-dioxo-butyrlic acid	297.1121	297.1127
4-[3-(2-cyanobenzyl)phenyl]-2,4-dioxo-butyrlic acid	NH ₄ ⁺ 325.1183	325.1157

Methyl 4-[3-benzylphenyl]- 2,4-dioxobutyrates	C ₁₈ H ₁₆ O ₄ 297.1121	297.113
4-[3-(3,5-dichloro-benzyl)- phenyl]-2,4-dioxo-butyric acid	351.0185	351.0167
4-(5-benzyl-2,4- dimethylphenyl)-2,4-dioxo- butyric acid	311.1278	311.1298
4-(5-benzyl-2- methylphenyl)-2,4-dioxo- butyric acid	297.1121	297.1123
4-(3-cyclohexylmethyl- phenyl)-2,4-dioxo-butyric acid	289.1434	289.1449
4-[3-[(methyl-phenyl- amino)-methyl]-phenyl]- 2,4-dioxo-butyric acid	312.123	312.1235

4-[3-benzyl-5-(5-hydroxy-pentyl)-phenyl]-2,4-dioxo-butyrlic acid	369.1696	369.1688
4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyrlic acid	NH ₄ ⁺ 378.1448	378.1455
4-[3-(3-tert-butoxy-2-hydroxy-propyl)-5-(2-methyl-benzyl)-phenyl]-2,4-dioxo-butyrlic acid	427.2115	427.213
2,4-dioxo-4-[3-(2,3-dimethoxy-benzyl)-phenyl]-butyrlic acid	NH ₄ ⁺ 360.1442	360.1451
4-[3-(methoxyphenyl-methyl)phenyl]-2,4-dioxobutyric acid	C ₁₈ H ₁₆ O ₅ .NH ₄ ⁺ 330.1336	330.1344

4-[3-[hydroxy-(tetrahydro-
furan-3-yl)-methyl]-5-(2-
methyl-benzyl)-phenyl]-2,4-
dioxo-butyric acid

C₂₃H₂₄O₆.NH₄⁺
414.1917

414.1911

2,4-dioxo-4-(3-
phenoxy-methyl-phenyl)-
butyric acid

299.0914

299.0924

2,4-dioxo-4-(3-
phenoxy-methyl-phenyl)-
butyric acid methyl ester

313.107

313.1096

4-[3-benzyl-5-
(cyclopropylcarboxamido)-
phenyl]-2,4-dioxobutyric
acid

C₂₁H₉NO₅.NH₄⁺
383.1601

383.1601

4-[3-benzyl-5-(t-
butoxycarbonyl)phenyl]-
2,4-dioxobutyric acid

C₂₂H₂₃NO₆.NH₄⁺
415.1863

415.1867

4-[3-(hydroxy-phenyl-methyl)-phenyl]-2,4-dioxo-butyrlic acid	$C_{17}H_{14}O_5$ 299.0919	299.0905
4-(5-benzyl-2,3-dimethylphenyl)-2,4-dioxo-butyrlic acid sodium salt	311.1278	311.1275
N-[3-(3,5-dibromobenzyl)phenyl]-2,4-dioxo-butyrlic acid	$C_{17}H_{12}Br_2O_4 NH_4^+$ 455.9440	455.9461
4-[3-(2-methyl-benzyl)-5-pyrimidin-2-yl-phenyl]-2,4-dioxo-butyrlic acid methyl ester	389.1496	389.149
4-[3-benzyl-2-(pyrimidin-2-ylamino)-phenyl]-2,4-dioxo-butyrlic acid hydrochloride	$C_{21}H_{20}N_3O_4$ 376.1306	376.1292

4-[3-benzoimidazol-1-ylmethyl-5-(2-methylbenzyl)-phenyl]-2,4-dioxo-butyric acid TFA salt

427.1652

427.1648

2,4-dioxo-4-[3-(3-trifluoromethylbenzyl)phenyl]butyric acid

CHN +0.75 HCl
C:57.24; H: 3.67

C: 57.38;
H, 4.03

4-(4-phenoxy-phenyl)-2,4-dioxo-butyric acid

285.0757

285.0763

2,4-dioxo-4-(3-[1,2,3]triazol-2-ylmethyl-phenyl)-butyric acid

C₁₃H₁₁N₃O₄.Na
296.0642

296.0645

4-[3-benzyl-5-(6-methoxy-pyridin-2-yl)-phenyl]-2,4-dioxo-butyric acid

390.1336

390.1361

4-(3-benzotriazol-2-ylmethyl-phenyl)-2,4-dioxobutyric acid	324.0984	324.0978
4-{3-benzyl-5-(2-(4-methylpiperazin-1-yl)-pyrazin-6-yl)phenyl}-2,4-dioxobutyric acid	459.2027	459.2014
4-[4-(3-phenethyl)phenyl]-2,4-dioxobutyric acid	297.1121	297.1124
4-[4-(3-chlorobenzyl)phenyl]-2,4-dioxobutyric acid	C ₁₇ H ₁₃ ClO ₄ .NH ₄ ⁺ 334.0841	334.0854
4-(3-benzoimidazol-1-ylmethyl-phenyl)-2,4-dioxobutyric acid trifluoroacetic acid salt	323.1026	323.1033

4-[3-benzyloxy-5-(6-tert-butoxycarbonylamino-hexyloxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid methyl ester	528.2604	528.2592
4-(3-benzotriazol-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid	274.0822	274.0825
4-[3-(3,5-dimethyl-pyrazol-1-ylmethyl)-phenyl]-2,4-dioxo-butyric acid	C ₁₆ H ₁₆ N ₂ O ₄ 301.1183	301.1196
4-[3-benzyloxy-5-(2-morpholin-4-yl-ethoxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid TFA salt	428.1704	428.1695
4-(4-methyl-3-phenoxy-phenyl)-2,4-dioxo-butyric acid	299.0914	299.0914

4-[3-(2-hydroxy-benzyl)-
phenyl]-2,4-dioxo-butyric
acid

316.118

316.1177

4-[3-benzyl-5-(6-
dimethylamino-pyrazin-2-
yl)-phenyl]-2,4-dioxo-
butyric acid

404.1605

404.162

EXAMPLE 116

HIV Integrase Assay: Strand Transfer Catalyzed by Recombinant Integrase and Preintegration Complexes

Assays for the strand transfer activity of integrase were
5 conducted according to Wolfe, A.L. et al., J. Virol. 70, 1424 (1996), and
Farnet, C.M. and Bushman F.D. (1997) Cell; 88, 483 for recombinant
integrase and preintegration complexes, respectively, hereby
incorporated by reference for these purposes.

Representative compounds tested in the integrase assay
10 demonstrated IC₅₀'s less than 1 micromolar. Further, representative
compounds tested in the preintegration complex assay also
demonstrated IC₅₀'s of less than 1 micromolar.

EXAMPLE 117

15 Assay for inhibition of HIV replication

Assays for the inhibition of acute HIV infection of T-
lymphoid cells was conducted according to Vacca, J.P. et al., (1994),
Proc. Natl. Acad. Sci. USA 91, 4906, herein incorporated by reference for
these purposes.

20 Representative compounds tested in the present assay
demonstrated IC₉₅s of less than 10 micromolar.

EXAMPLE 118

Oral Composition

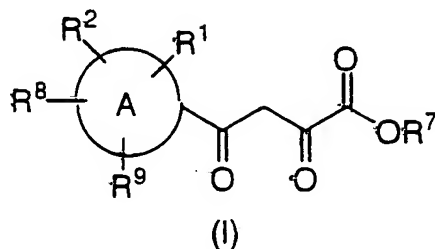
25 As a specific embodiment of an oral composition of a
compound of this invention, 50 mg of a compound of the present
invention is formatted with sufficient finely divided lactose to provide a
total amount of 580 to 590 mg to fill a size 0 hard gelatin capsule.

30 While the foregoing specification teaches the principles of
the present invention, with examples provided for the purpose of
illustration, it will be understood that the practice of the invention
encompasses all of the usual variations, adoptions, or modifications, as
come within the scope of the following claims and their equivalents.

35

WHAT IS CLAIMED:

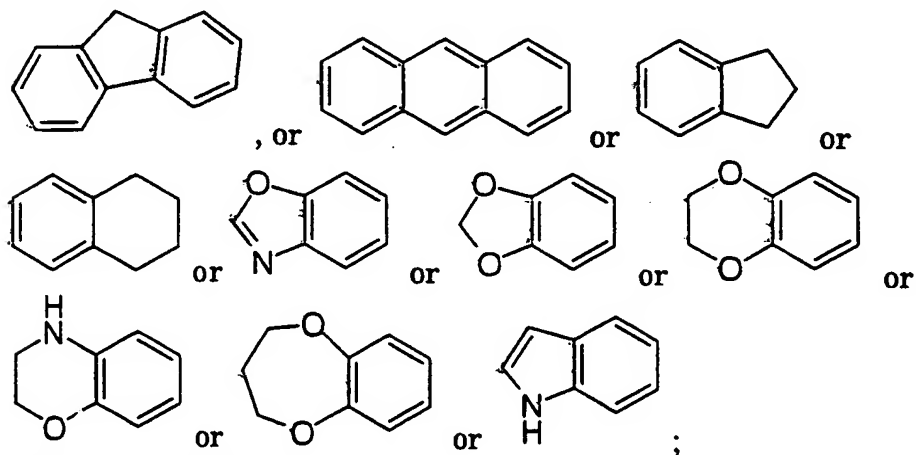
1. A compound of structural formula (I):



and tautomers and pharmaceutically acceptable salts thereof,
 5 wherein:

A is a six-membered aromatic or heteroaromatic ring containing 0, 1, or 2 nitrogen heteroatoms substituted on carbon or nitrogen by R¹, R², R⁸, and R⁹;

optionally the aromatic ring may be fused with another ring system to
 10 form:



R¹ is selected from:

- 15 (1) -H,
 (2) -C₁₋₅ alkyl,
 (3) -C₁₋₆ alkyl-OR⁷,
 (4) -O-C₁₋₆ alkyl-OR⁷,
 (5) -O-C₁₋₆ alkyl-SR⁷,
 20 (6) -CF₃ or -CH₂CF₃,
 (7) -halo,
 (8) -NO₂,

- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
 (10) -R⁶,
 (11) -C₂₋₅ alkenyl-R³,
 (12) -C₂₋₅ alkynyl-R³,
 5 (13) -O-R⁶,
 (14) -O-C₁₋₆ alkyl, wherein one or more of the hydrogen atoms
 may be replaced with fluorine atoms,
 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷;
 (16) -O-C₂₋₆ alkyl-N(R⁴)(R⁵);
 10 (17) -S-C₁₋₃ alkyl;
 (18) -C(O)CH₂C(O)C(O)OR⁷;
 (19) -CH₂-CH(OH)-CH₂-O-R⁷; and
 (20) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

- 15 (1) -H,
 (2) -R³,
 (3) -C₁₋₆ alkyl,
 (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the
 hydrogen atoms on C₁₋₆ alkyl may be replaced with a
 20 fluorine atom,
 (5) -C₂₋₆ alkenyl,
 (6) -O-R⁶,
 (7) -O-C₁₋₆ alkyl-OR⁶,
 (8) -O-C₁₋₆ alkyl-SR⁶,
 25 (9) -S(O)_n-R⁶,
 (10) -C₁₋₆ alkyl (OR⁶)(R⁴),
 (11) -C₀₋₆ alkyl-N(R⁴)(R⁶),
 (12) -C₁₋₆ alkyl S(O)_n-R⁶,
 (13) -C₀₋₆ alkyl C(O)-R⁶,
 30 (14) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
 (15) -C₁₋₆ alkyl C(S)-R⁶,
 (16) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
 (17) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
 (18) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- 5 (1) a 5 or 6 membered aromatic or heteroaromatic ring, containing 0, 1, 2, 3, or 4 heteroatoms selected from oxygen, nitrogen and sulfur, unsubstituted or substituted on nitrogen or carbon by 1 to 5 substituents selected from:
- 10 (a) halogen,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 15 (d) phenyl,
 (e) -S-C₁₋₆ alkyl,
 (f) -CN,
 (g) hydroxy,
 (h) phenyloxy,
 (i) -C₀₋₆ alkyl-N(R⁷)₂,
- $$\text{---N} \begin{array}{c} \diagup \quad \diagdown \\ | \quad | \\ \diagdown \quad \diagup \end{array} \text{N-CH}_3$$
- (j) ,
 (k) oxo, and
 20 (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;
- 25 (2) a 3 to 6 membered saturated ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, unsubstituted or substituted with 1 to 5 substituents selected from:
- 30 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ alkyloxy-,
 (d) -CF₃,
 (e) -OCF₃,

- (f) -CN,
 - (g) =O,
 - (h) benzyl, and
 - (i) hydroxy;
- 5 (3) unsubstituted or substituted hexahydrothieno[3,4-d]imidazolyl with one or two substituents selected from:
- (a) oxo,
 - (b) halogen,
 - (c) C₁₋₆ alkyl,
 - 10 (d) C₁₋₆ alkyloxy-,
 - (e) -CF₃,
 - (f) -OCF₃,
 - (g) -CN, and
 - (h) hydroxy;
- 15 (4) a 5 or 6 membered aromatic or heteroaromatic ring, containing 0, 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulfur, fused with a phenyl ring; wherein the ring system is unsubstituted or substituted on a nitrogen or carbon atom by 1 to 3 substituents selected from:
- 20 (a) -halogen,
 - (b) -C₁₋₆ alkyl,
 - (c) -C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - 25 (f) -CN, and
 - (g) -hydroxy;
- (5) a 3 to 6 membered saturated ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, fused with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:
- 30 (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - 35 (e) -OCF₃,

- (f) -CN,
(g) =O, and
(h) hydroxy;
- 5 (6) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms
selected from oxygen, nitrogen or sulfur, containing 2 or 3
double bonds, unsubstituted or substituted with 1 or 2
substituents selected from:
- (a) halogen,
(b) C₁₋₆ alkyl,
10 (c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O, and
15 (h) hydroxy; and
- (7) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms
selected from oxygen, nitrogen or sulfur, containing 2 or 3
double bonds, fused with a phenyl ring, unsubstituted or
substituted with 1 or 2 substituents selected from:
- 20 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
25 (f) -CN,
(g) =O, and
(h) hydroxy; and
- each R⁴ is independently selected from:
- 30 (1) -H,
(2) -C₁₋₄ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₂₋₃ alkenyl,
(6) -C₁₋₃ alkyl-R³,
35 (7) -C₂₋₃ alkenyl-R³,

(8) $-S(O)_n-R^3$, and

(9) $-C(O)-R^3$;

each R^5 is independently selected from:

- (1) $-H$,
- 5 (2) $-C_{1-3}$ alkyl,
- (3) $-CF_3$,
- (4) $-R^3$,
- (5) $-C_{2-3}$ alkenyl,
- (6) $-C_{1-3}$ alkyl- R^3 ,
- 10 (7) $-C_{2-3}$ alkenyl- R^3 ,
- (8) $-S(O)_n-R^3$,
- (9) $-C(O)-R^3$,
- (10) $-C(O)OR^4$, and
- (11) $-C(O)C(O)OH$;

15 each R^6 is independently selected from:

- (1) $-C_{1-3}$ alkyl- R^3 , and
- (2) $-R^3$;

each R^7 is independently selected from:

- (1) $-H$, and
- 20 (2) $-C_{1-6}$ alkyl;

R^8 is selected from:

- (1) $-H$,
- (2) $-O-C_{1-6}$ alkyl and
- (3) C_{1-6} alkyl;

25 R^9 is selected from:

- (1) $-H$,
- (2) $-O-C_{1-3}$ alkyl,
- (3) $-OH$, and
- (4) oxo; and

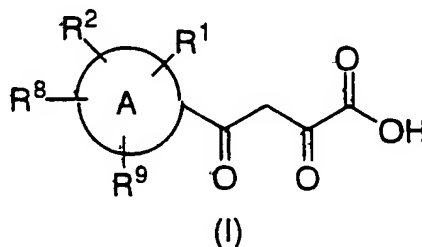
30 each n is independently selected from 0, 1 and 2;

PROVIDED THAT when A is phenyl:

- (1) R^1 is not R^6 para to the dioxobutyric acid/ester moiety; and
- (2) R^2 is not selected from:

- 5
- (a) phenyl para to the dioxobutyric acid/ester moiety,
 (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 (c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and
 (d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- (3) at least one of R¹, R², and R⁸ is not:
- 10 (a) -H,
 (b) C₁₋₆ alkyl, or
 (c) R³ wherein R³ is cycloalkyl; and
- (4) and when R² is S(O)_nR⁶, and R⁶ is CH₂-R³ or R³, then R³ is not unsubstituted phenyl.

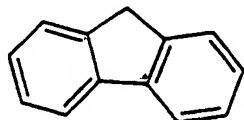
15 2. The compound according to Claim 1 of structural formula:



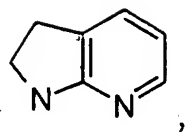
and tautomers and pharmaceutically acceptable salts thereof, wherein:

20 A is selected from:

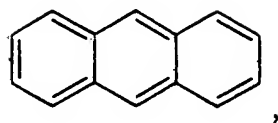
- (1) phenyl,
 (2) pyridyl,
 (3) naphthyl,
 (4) indolyl, provided that the aryl ring is substituted by the
 25 dioxobutyric acid/ester moiety in structural formula (I),
 (5)



(6)

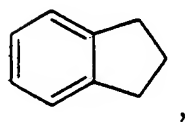


(7)

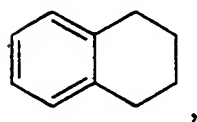


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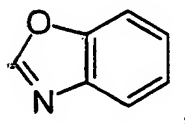
(8)



(9)

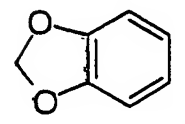


(10)

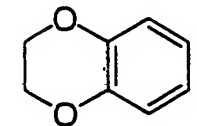


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(11)

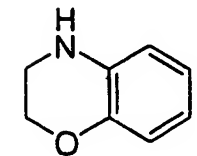


(12)

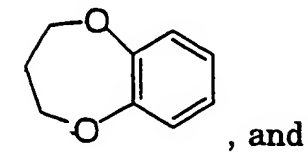


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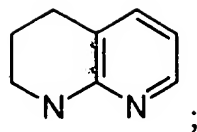
(13)



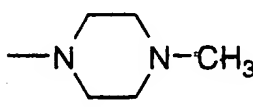
(14)



(15)

R¹ is selected from:

- (1) -H,
- 5 (2) -C₁₋₅ alkyl,
- (3) -C₁₋₆ alkyl-OR⁷;
- (4) -O-C₁₋₆ alkyl-OR⁷,
- (5) -O-C₁₋₆ alkyl-SR⁷,
- (6) -CF₃ or -CH₂CF₃,
- 10 (7) -F, Cl, or Br,,
- (8) -NO₂,
- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -phenyl,
- 15 (11) substituted phenyl substituted with 1 or 2 substituents
independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) phenyl,
 - 20 (e) -CF₃,
 - (f) -OCF₃,
 - (g) -CN,
 - (h) hydroxy,
 - (i) phenyloxy, and
 - 25 (j) substituted phenyloxy with 1, 2, or 3 substituents
selected from:
 - (i) halogen,
 - (ii) -C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - 30 (iv) hydroxy;
- (12) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:

- 5 (a) halogen,
 (b) C₁₋₆ alkyl,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (d) phenyl,
 (e) -CF₃,
 (f) -SCH₃,
 (g) -CN,
 (h) hydroxy,
 10 (i) phenyloxy,
 (j) -C₀₋₆ alkyl-N(R⁷)₂,
 (k)
- 

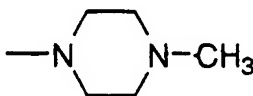
, and
- 15 (l) substituted phenyloxy with 1, 2, or 3 substituents
 selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 (iv) hydroxy;
- 20 (13) -O-R⁶,
 (14) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three
 fluorine atoms,
 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷;
 (16) -O-C₂₋₆ alkyl-N(R⁴)(R⁵);
 25 (17) -S-C₁₋₃ alkyl;
 (18) -C(O)CH₂C(O)C(O)OR⁷;
 (19) -CH₂-CH(OH)-CH₂-O-R⁷; and
 (20) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

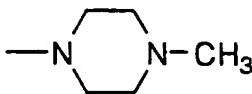
- 30 (1) -H,
 (2) -R³,
 (3) -C₁₋₆ alkyl,

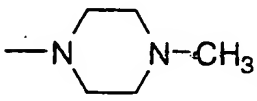
- (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the hydrogen atoms on C₁₋₆ alkyl may be replaced with a fluorine atom,
- (5) -O-R⁶,
- 5 (6) -S-R⁶,
- (7) -O-C₁₋₆ alkyl-SR⁶;
- (8) -C₁₋₆ alkyl (OR⁶)(R⁴),
- (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (10) -C₁₋₆ alkyl S-R⁶,
- 10 (11) -C₀₋₆ alkyl C(O)-R⁶,
- (12) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- (13) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- (14) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (15) -CH₂(OR⁷)-R⁶;

15 each R³ is independently selected from:

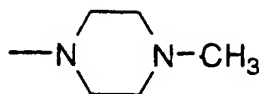
- (1) phenyl;
- (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
- 20 (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- 25 (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- (g) hydroxy,
- (h) phenyloxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,
- 30 (j)
- 

The structure shows a six-membered ring (piperidine) with a nitrogen atom at the bottom-left position. A bond extends from the nitrogen atom to the left, and another bond extends from the nitrogen atom to the right, where it is connected to a methyl group (-CH₃).
- (k) oxo, and

- (1) substituted phenyloxy with 1, 2, or 3 substituents selected from:
- (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- (3) thienyl,
- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)
- 
- (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
- (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- (5) pyridyl,
- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,

- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 5 (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- (g) hydroxy,
- (h) phenyloxy,
- 10 (i) -C₀₋₆ alkyl-N(R⁷)₂,
- (j)
- 
- (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
- 15 (i) halogen,
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;
- 20 (7) imidazolyl,
- (8) substituted imidazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 25 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- 30 (f) -CN,
- (g) hydroxy,
- (h) phenyloxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,

(j)



(k) oxo, and

(l) substituted phenoxy with 1, 2, or 3 substituents selected from:

- (i) halogen,
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;

5

10

(9) pyrrolyl,

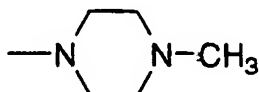
(10) substituted pyrrolyl substituted on carbon with one or two substituents independently selected from:

- (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- (g) hydroxy,
- (h) phenoxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,

15

20

(j)



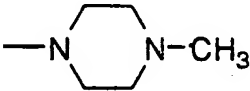
25

(k) oxo, and

(l) substituted phenoxy with 1, 2, or 3 substituents selected from:

- (i) halogen,
- (ii) C₁₋₆ alkyl,
- (iii) -CF₃, and
- (iv) hydroxy;

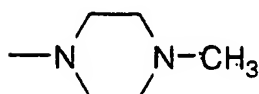
30

- (11) pyrazolyl,
- (12) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
 - 5 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - 10 (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenoxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - 15 (j)
- 
*N1CCN(C)CC1
- (k) oxo, and
 - (l) substituted phenoxy with 1, 2, or 3 substituents selected from:
 - 20 (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- (15) piperidinyl,
- 25 (16) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - 30 (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O,

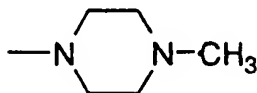
- (h) benzyl, and
(i) hydroxy;
- (17) morpholinyl,
- (18) substituted morpholinyl substituted at a carbon or nitrogen
5 atom with 1 or 2 substituents independently selected from:
(a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
10 (e) -OCF₃,
(f) -CN,
(g) =O,
(h) benzyl, and
(i) hydroxy;
- (19) hexahydrothieno[3,4-d]imidazolyl,
- (20) substituted hexahydrothieno[3,4-d] substituted
hexahydrothieno[3,4-d]imidazolyl with one or two
substituents independently selected from:
(a) oxo,
20 (b) halogen,
(c) C₁₋₆ alkyl,
(d) C₁₋₆ alkyloxy-,
(e) -CF₃,
(f) -OCF₃,
25 (g) -CN, and
(h) hydroxy,
- (21) naphthyl,
- (22) substituted naphthyl with 1, 2, or 3 substituents
independently selected from:
30 (a) -halogen,
(b) -C₁₋₆ alkyl,
(c) -C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
35 (f) -CN, and

- (g) -hydroxy,
- (23) indolyl,
- (24) substituted indolyl substituted on a carbon atom with one or two substituents independently selected from:
- 5 (a) -halogen,
- (b) -C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- (e) -OCF₃,
- 10 (f) -CN, and
- (g) -hydroxy;
- (25) C₃₋₆ cycloalkyl fused with a phenyl ring
- (26) substituted C₃₋₆ cycloalkyl fused with a phenyl ring substituted on carbon with one or two substituents independently selected from:
- 15 (a) halogen,
- (b) C₁₋₆ alkyl,
- (c) C₁₋₆ alkyloxy-,
- (d) -CF₃,
- 20 (e) -OCF₃,
- (f) -CN,
- (g) =O, and
- (h) hydroxy;
- (27) pyrazinyl;
- 25 (28) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 30 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) phenyl,
- (e) -S-C₁₋₆ alkyl,
- (f) -CN,
- 35 (g) hydroxy,

- (h) phenyloxy,
- (i) -C₀₋₆ alkyl-N(R⁷)₂,
- (j)



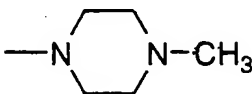
- 5 (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - 10 (iii) -CF₃, and
 - (iv) hydroxy;
- (29) pyrimidinyl;
- (30) substituted pyrimidinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
 - 15 (a) halogen,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - 20 (d) phenyl,
 - (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - 25 (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)



- (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,

30

- (iii) -CF₃, and
 (iv) hydroxy;
- (31) triazolyl;
- (32) substituted triazolyl with one or two substituents
 5 independently selected from:
- (a) halogen,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 10 atoms may be replaced with a fluorine atom,
 (d) phenyl,
 (e) -S-C₁₋₆ alkyl,
 (f) -CN,
 (g) hydroxy,
 15 (h) phenyloxy,
 (i) -C₀₋₆ alkyl-N(R⁷)₂,
 (j)
-
- (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents
 20 selected from:
- (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 25 (iv) hydroxy;
- (33) tetrazolyl;
- (34) substituted tetrazolyl with a substituent selected from:
- (a) halogen,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 30 atoms may be replaced with a fluorine atom,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (d) phenyl,

- 5
- (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,
 - (j)
- 
- 10
- (k) oxo, and
 - (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
 - (i) halogen,
 - (ii) C₁₋₆ alkyl,
 - (iii) -CF₃, and
 - (iv) hydroxy;
- 15
- (35) C₃₋₆ cycloalkyl;
 - (36) substituted C₃₋₆ cycloalkyl substituted with one or two substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O,
 - (h) benzyl, and
 - (i) hydroxy;
- 20
- (37) tetrahydrofuran;
 - (38) substituted tetrahydrofuran substituted with one or two substituents independently selected from:
 - (a) halogen,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
- 25
- 30

- (e) -OCF₃,
(f) -CN,
(g) =O,
(h) benzyl, and
5 (i) hydroxy;
(39) piperazinyl;
(40) substituted piperazinyl substituted with one or two
substituents independently selected from:
(a) halogen,
10 (b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
15 (g) =O,
(h) benzyl, and
(i) hydroxy;
(41) benzotriazolyl,
(42) substituted benzotriazolyl substituted on a carbon atom with
20 one or two substituents independently selected from:
(a) -halogen,
(b) -C₁₋₆ alkyl,
(c) -C₁₋₆ alkyloxy-,
(d) -CF₃,
25 (e) -OCF₃,
(f) -CN, and
(g) -hydroxy;
(43) benzoimidazolyl,
(44) substituted benzoimidazolyl substituted on a carbon atom
30 with one or two substituents independently selected from:
(a) -halogen,
(b) -C₁₋₆ alkyl,
(c) -C₁₋₆ alkyloxy-,
(d) -CF₃,

- (e) -OCF₃,
- (f) -CN, and
- (g) -hydroxy;

each R⁴ is independently selected from:

- 5 (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₂₋₃ alkenyl,
- 10 (6) -C₁₋₃ alkyl-R³,
- (7) -C₂₋₃ alkenyl-R³, and
- (8) -C(O)-R³;

each R⁵ is independently selected from:

- (1) -H,
- 15 (2) -C₁₋₃ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₃ alkyl-R³,
- 20 (7) -S(O)_n-R³,
- (8) -C(O)-R³,
- (9) -C(O)OR⁴, and
- (10) -C(O)C(O)OH;

each R⁶ is independently selected from:

- 25 (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

each R⁷ is independently selected from:

- (1) -H, and
- (2) -C₁₋₆ alkyl;

30 R⁸ is selected from hydrogen, methyl and -O- C₁₋₆ alkyl; and

R⁹ is selected from:

- (1) -H,
- (2) -O- C₁₋₃ alkyl,
- (3) -OH, and

(4) oxo; and
each n is independently selected from 0, 1 and 2;

PROVIDED THAT when A is phenyl:

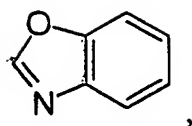
- 5 (1) R¹ is not :
- (a) phenyl para to the dioxobutyric acid/ester moiety,
 - (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 - (c) C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety, or
 - 10 (d) substituted -C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- (2) R² is not selected from:
- (a) phenyl para to the dioxobutyric acid/ester moiety,
 - 15 (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 - (c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and
 - (d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
 - 20 (3) at least one of R¹, R², and R⁸ is not:
- (a) -H,
 - (b) C₁₋₆ alkyl, or
 - (c) R³ wherein R³ is cycloalkyl; and
 - 25 (4) and when or R² is SR⁶, and R⁶ is CH₂-R³ or R³,
then R³ is not unsubstituted phenyl.

3. The compound according to Claim 2 , and tautomers and pharmaceutically acceptable salts thereof, wherein:

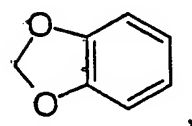
30 A is selected from:

- (1) phenyl,
- (2) pyridinyl,
- (3) indolyl, provided that 6-membered aromatic ring is substituted by the dioxobutyric moiety in structural formula
- 35 (I);

(4)

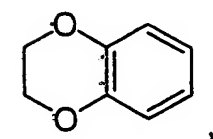


(5)

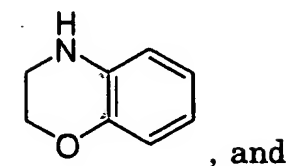


5

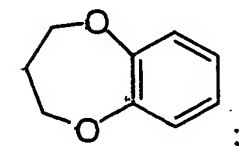
(6)



(7)



(8)



10

R¹ is selected from:

- (1) -H,
- (2) -CH₃,
- (3) -C₁₋₆ alkyl-OR⁷;
- 15 (4) -O-C₁₋₆ alkyl-OR⁷,
- (5) -O-C₁₋₆ alkyl-SR⁷,
- (6) -CF₃ or -CH₂CF₃,
- (7) -Cl,
- (8) -F,
- 20 (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -phenyl,
- (11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:
- 25 (a) -F, -Cl, or -Br,

- 5 (b) CH_3 ,
 (c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-\text{CF}_3$,
 (e) $-\text{SCH}_3$,
 (f) $-\text{CN}$,
 (g) hydroxy, and
 (h) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^7)_2$,
 (12) $-\text{O}-\text{CH}_2$ -phenyl, wherein the phenyl group may be
 10 unsubstituted or substituted with 1 to four substituents
 independently selected from:
 (a) $-\text{F}$, $-\text{Cl}$, or $-\text{Br}$,
 (b) CH_3 ,
 (c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-\text{CF}_3$,
 15 (e) $-\text{SCH}_3$,
 (f) $-\text{CN}$,
 (g) hydroxy, and
 (h) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^7)_2$,
 (13) $-\text{O}-\text{C}_{1-6}$ alkyl, unsubstituted or substituted with one to three
 20 fluorine atoms,
 (14) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$;
 (15) $-\text{O}-\text{C}_{1-6}$ alkyl- $\text{NH}-\text{C}(\text{O})-\text{OR}^7$;
 (16) $-\text{O}-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$,
 (17) $-\text{O}-\text{CH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$,
 25 (18) $-\text{O}-\text{CH}_2\text{CH}_2\text{NH}_2$,
 (19) $-\text{O}-\text{CH}(\text{CH}_3)\text{CH}_2\text{NH}_2$,
 (20) $-\text{S}-\text{CH}_3$,
 (21) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$,
 (22) $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}^7$, and
 30 (23) $-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}_2\text{N}(\text{R}^4)(\text{R}^5)$;

R^2 is selected from:

- (1) $-\text{H}$,
 (2) $-\text{R}^3$,
 (3) $-\text{CH}_3$,

- (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the hydrogen atoms on C₁₋₆ alkyl may be replaced with a fluorine atom,
- (5) -O-R⁶,
- 5 (6) -S-R⁶,
- (7) -O-C₁₋₆ alkyl-SR⁶;
- (8) -C₁₋₆ alkyl (OR⁶)(R⁴),
- (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (10) -C₀₋₆ alkyl C(O)-R⁶,
- 10 (11) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- (12) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- (13) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (14) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- 15 (1) phenyl;
- (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, -Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
- 20 atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,-,
- (d) -CN,
- (e) hydroxy, and
- 25 (f) oxo;
- (3) thienyl,
- (4) substituted thienyl-substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from F, Cl, and Br,
- 30 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- (5) pyridyl,

- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) hydroxy, and
 - (e) oxo;
- (7) imidazolyl,
- (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) -CH₃,
 - (c) -CF₃,
 - (d) -OCH₃,
 - (e) -OCF₃, and
 - (f) hydroxy;
- (11) C₃₋₆ cycloalkyl,
- (12) substituted C₃₋₆ cycloalkyl with 1 or 2 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) CH₃,
 - (c) methyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O, and
 - (h) hydroxy;
- (13) piperidinyl,
- (14) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen selected from -F, -Cl, and -Br,

- (b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
5 (f) =O, and
(g) hydroxy;
(15) morpholinyl,
(16) substituted morpholinyl substituted on carbon or nitrogen
with 1 or 2 substituents independently selected from:
10 (a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃, and
15 (f) hydroxy;
(17) hexahydrothieno[3,4-d]imidazolyl,
(18) naphthyl,
(19) substituted naphthyl with 1, 2, or 3 substituents
independently selected from:
20 (a) -halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
25 (f) -CN, and
(g) -hydroxy,
(20) indolyl, and
(21) 1,2,3,4-tetrahydronaphthalenyl,
(22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on
30 carbon with a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
35 (e) -OCF₃,

- (f) -CN,
 (g) =O, and
 (h) hydroxy;
- (23) pyrazinyl;
- 5 (24) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 10 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 (d) hydroxy,
 (e) phenoxy,
 (f) -C₀₋₆ alkyl-N(R⁷)₂, and
 15 (g)
- The chemical structure shows a six-membered piperazine ring. One nitrogen atom is bonded to a methyl group (-CH₃). The other nitrogen atom is bonded to a substituent, represented by a single bond extending to the left. The structure is enclosed in a box.
- (25) pyrimidinyl;
- (26) substituted pyrimidinyl substituted on nitrogen or carbon with a substituent selected from:
- 20 (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-, and
 (d) phenyl,
- (27) triazolyl;
- 25 (28) substituted triazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-, and
 (d) hydroxy,
- 30 (29) tetrazolyl;
- (30) substituted tetrazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,

- (c) methoxy-, and
- (d) hydroxy,
- (31) C₃₋₆ cycloalkyl;
- (32) substituted C₃₋₆ cycloalkyl substituted with one or two
5 substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - 10 (e) -OCF₃,
- (33) tetrahydrofuran;
- (34) substituted tetrahydrofuran substituted with one or two
substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - 15 (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (35) piperazinyl;
- 20 (36) substituted piperazinyl substituted with one or two
substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - 25 (d) -CF₃,
 - (e) -OCF₃,
 - (f) benzyl, and
 - (g) hydroxy;
- (37) benzotriazolyl,
- 30 (38) substituted benzotriazolyl substituted on carbon with one or
two substituents independently selected from:
 - (a) -halogen, selected from -F, -Cl, and -Br,
 - (b) -methyl,
 - (c) methoxy-,
 - 35 (d) -CF₃, and

- (e) -OCF₃,
(39) benzoimidazolyl, and
(40) substituted benzoimidazolyl substituted on carbon with one or two substituents independently selected from:
- 5 (a) -halogen, selected from -F, -Cl. and -Br,
(b) -methyl,
(c) methoxy-,
(d) -CF₃, and
(e) -OCF₃;
- 10 each R⁴ is independently selected from:
- (1) -H,
(2) -C₁₋₄ alkyl,
(3) -CF₃,
(4) -R³,
15 (5) -C₁₋₃ alkyl-R³, and
(6) -C(O)-R³;
- each R⁵ is independently selected from:
- (1) -H,
(2) -C₁₋₃ alkyl,
20 (3) -CF₃,
(4) -R³,
(5) -C₁₋₃ alkyl-R³,
(6) -C(O)-R³,
(7) -C(O)OR⁴, and
25 (8) -C(O)C(O)OH;
- each R⁶ is independently selected from:
- (1) -C₁₋₃ alkyl-R³, and
(2) -R³;
- each R⁷ is independently selected from:
- 30 (1) -H, and
(2) -C₁₋₆ alkyl;
- R⁸ is selected from hydrogen, methyl and -O- C₁₋₆ alkyl; and
R⁹ is selected from:
- (1) -H,

(2) -O- C₁₋₃ alkyl,

(3) -OH, and

(4) oxo; and

5 PROVIDED THAT: when A is phenyl,

(1) R¹ is not :

(a) phenyl para to the dioxobutyric acid/ester moiety,

(b) substituted phenyl para to the dioxobutyric acid/ester moiety,

10 (c) C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety, or

(d) substituted -C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety; and

(2) R² is not selected from:

15 (a) phenyl para to the dioxobutyric acid/ester moiety,

(b) substituted phenyl para to the dioxobutyric acid/ester moiety,

(c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and

20 (d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and

(3) at least one of R¹, R², and R⁸ is not:

(a) -H,

(b) C₁₋₆ alkyl, or

25 (c) R₃ wherein R₃ is cycloalkyl; and

(4) and when R² is SR⁶, R⁶ is R₃.

4. The compound according to Claim 3 and tautomers and pharmaceutically acceptable salts thereof, wherein:

30 R¹ is selected from:

(1) -H,

(2) -CH₃,

(3) -CH₂OCH₃,

(4) -OCH₂CH₂OH,

- (5) $-\text{OCH}_2\text{CH}_2\text{OCH}_3$,
 (6) $-(\text{CH}_2)_6-\text{OH}$,
 (7) $-\text{CF}_3$,
 (8) $-\text{F}$,
 5 (9) $-\text{Cl}$,
 (10) $-\text{C}_{0-3}$ alkyl $-\text{N}(\text{R}^4)(\text{R}^5)$,
 (11) $-\text{phenyl}$,
 (12) phenyl C_{1-3} alkyl-, wherein the phenyl group may be
 unsubstituted or substituted with 1 to four substituents
 10 independently selected from:
 (a) $-\text{F}$, $-\text{Cl}$, or $-\text{Br}$,
 (b) CH_3 ,
 (c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-\text{CF}_3$,
 15 (e) $-\text{CN}$,
 (f) hydroxy,
 (g) $-\text{C}_{0-6}$ alkyl $-\text{N}(\text{R}^7)_2$,
 (13) $-\text{O}-\text{CH}_2$ -phenyl, wherein the phenyl group may be
 unsubstituted or substituted with 1 to four substituents
 20 independently selected from:
 (a) $-\text{F}$, $-\text{Cl}$, or $-\text{Br}$,
 (b) CH_3 ,
 (c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-\text{CF}_3$,
 25 (e) $-\text{CN}$,
 (f) hydroxy,
 (g) $-\text{C}_{0-6}$ alkyl $-\text{N}(\text{R}^7)_2$,
 (14) $-\text{O}-\text{CH}_3$,
 (15) $-\text{OCH}_2\text{CH}_3$,
 30 (16) $-\text{OCH}_2\text{CF}_3$,
 (17) $-\text{OCF}_3$,
 (18) $-\text{OCH}(\text{CH}_3)_2$,
 (19) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$,
 (20) $-\text{O}-\text{C}_{1-6}$ alkyl $-\text{NH}-\text{C}(\text{O})-\text{OR}^7$,

- (21) $-O-CH_2CH_2 N(CH_3)_2$,
 (22) $-O-CH(CH_3)CH_2N(CH_3)_2$,
 (23) $-O-CH_2CH_2 NH_2$,
 (24) $-O-CH(CH_3)CH_2NH_2$,
 5 (25) $-S-CH_3$,
 (26) $-C(O)CH_2C(O)C(O)OH$,
 (27) $-CH_2-CH(OH)-CH_2-O-R^7$, and
 (28) $-C(OH)(CH_3)-CH_2N(R^4)(R^5)$;

R^2 is selected from:

- 10 (1) $-H$,
 (2) $-R^3$,
 (3) $-CH_2-R^3$,
 (4) $-CH_2CH_2-R^3$,
 (5) $-CF_2-R^3$,
 15 (6) $-CH(CH_3)-R^3$,
 (7) $-O-R^6$,
 (8) $-S$ -phenyl,
 (9) $-C_{1-6}$ alkyl $(OR^6)(R^4)$,
 (10) $-C_{0-6}$ alkyl- $N(R^4)(R^6)$,
 20 (11) $-C(O)-R^3$,
 (12) $-C_{0-6}$ alkyl $C(O)CH_2-C(O)-OH$,
 (13) $-C_{1-6}$ alkyl $NR^4C(O)-R^6$,
 (14) $-CH(OCH_3)R^3$, and
 (15) $-CH(OH)R^3$;

25 each R^3 is independently selected from:

- (1) phenyl;
 (2) substituted phenyl with 1, 2, or 3 substituents independently
 selected from:
 30 (a) halogen, selected from $-F$, $-Cl$, $-Br$,
 (b) $-CH_3$,
 (c) methyloxy-,
 (d) ethyloxy-,
 (e) $-OCH_2CF_3$,
 (f) $-OCF_2CH_3$,

- (g) -CF₃,
(h) -CH₂CF₃,
(i) -CF₂CH₃,
(j) -OCF₃,
5 (k) -CN, and
(l) hydroxy;
- (3) thienyl,
(4) substituted thienyl substituted on a carbon atom with a
substituent selected from:
- 10 (a) F,
(b) Cl, and
(c) methyl;
- (5) pyridyl,
(6) substituted pyridyl substituted on a carbon with a
substituent selected from:
- 15 (a) -F,
(b) -Cl,
(c) -CH₃,
(d) -CF₃,
20 (e) -OCH₃,
(f) -OCF₃,
(g) hydroxy, and
(h) oxo;
- (7) pyrazolyl
25 (8) substituted pyrazolyl substituted on carbon with one or two
substituents independently selected from:
- (a) -F,
(b) -Cl,
(c) -CH₃, and
30 (d) -CF₃;
- (9) C₃₋₆ cycloalkyl,
(10) piperidinyl,
(11) substituted piperidinyl substituted on-carbon with a
substituent selected from:

- (a) methoxy-,
 (b) -OCF₃,
 (c) =O, and
 (d) hydroxy;
- 5 (12) morpholinyl,
 (13) naphthyl,
 (14) 1,2,3,4-tetrahydronaphthalenyl,
 (15) pyrazinyl;
 (16) substituted pyrazinyl substituted on nitrogen or carbon with
 10 a substituent selected from:
 (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) -CF₃,
 (d) methoxy-,
 15 (e) -N(CH₃)₂, and
 (f)
- CN1CCN(C)CC1
- (17) pyrimidinyl,
 (18) [1,2,3]-triazolyl,
 20 (19) [1,2,4]-triazolyl,
 (20) tetrazolyl;
 (21) cyclopropyl,
 (22) cyclobutyl,
 (23) cyclopentyl,
 25 (24) cyclohexyl,
 (25) tetrahydrofuran,
 (26) piperazinyl,
 (27) substituted piperazinyl substituted with a substituent
 selected from:
 30 (a) -F,
 (b) -Cl,
 (c) methyl,
 (d) -CF₃, and

- (e) benzyl,
- (28) benzotriazolyl,
- (29) benzoimidazolyl,

each R⁴ is independently selected from:

- 5 (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₁₋₃ alkyl-R³, and
- 10 (6) -C(O)-R³;

each R⁵ is independently selected from:

- (1) -H,
- (2) -CH₃,
- (3) -CF₃,
- 15 (4) phenyl,
- (5) -benzyl,
- (6) -C(O)OR⁴, and
- (7) -C(O)C(O)OH;

each R⁶ is independently selected from:

- 20 (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

each R⁷ is independently selected from:

- (1) -H, and
- (2) -C₁₋₆ alkyl;

25 R⁸ is selected from:

- (1) -H,
- (2) methoxy, and
- (3) -C₁₋₆ alkyl, and

R⁹ is selected from:

- 30 (1) -H,
- (2) -O- C₁₋₃ alkyl,
- (3) -OH, and
- (4) oxo; and

PROVIDED THAT: when A is phenyl,

- 35 (1) R¹ is not :

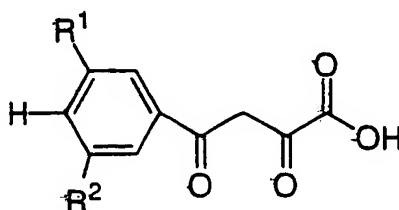
- 5
- (a) phenyl para to the dioxobutyric acid/ester moiety,
 - (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 - (c) C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety, or
 - (d) substituted -C₁₋₃ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- 10
- (2) R² is not selected from:
 - (a) phenyl para to the dioxobutyric acid/ester moiety,
 - (b) substituted phenyl para to the dioxobutyric acid/ester moiety,
 - (c) -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety, and
 - (d) substituted -C₁₋₆ alkyl phenyl para to the dioxobutyric acid/ester moiety; and
- 15
- (3) at least one of R¹, R², R⁸ and R⁹ is not:
 - (a) -H,
 - (b) C₁₋₆ alkyl, or
 - (c) R₃ wherein R₃ is cycloalkyl.

20

5. The compound according to Claim 4, wherein A is phenyl, and at least one of R¹, R², R⁸ and R⁹ is not hydrogen, and tautomers and pharmaceutically acceptable salts thereof.

25

6. The compound according to Claim 1 of structural formula:



and tautomers and pharmaceutically acceptable salts thereof, wherein: R¹ is selected from:

30

- (1) -H,

- (2) -CH₃,
(3) -C₁₋₆ alkyl-OR⁷;
(4) -O-C₁₋₆ alkyl-OR⁷,
(5) -O-C₁₋₆ alkyl-SR⁷,
5 (6) -CF₃ or -CH₂CF₃,
(7) -Cl,
(8) -F,
(9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
(10) -phenyl,
10 (11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:
(a) -F, -Cl, or -Br,
(b) -CH₃,
15 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
(e) -CF₃,
(f) -SCH₃,
(g) -CN,
(h) hydroxy,
20 (i) -C₀₋₆ alkyl-N(R⁷)₂,
(12) -O-CH₂-phenyl, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:
(a) -F, -Cl, or -Br,
25 (b) CH₃,
(c) -OCH₃, -OCH₂CH₃, -OCF₃, or -OCH₂CF₃,
(e) -CF₃,
(f) -SCH₃,
(g) -CN,
30 (h) hydroxy,
(i) -C₀₋₆ alkyl-N(R⁷)₂,
(13) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three
fluorine atoms,
(14) -C(O)CH₂C(O)C(O)OH,

- (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
 (16) -O-CH₂CH₂ N(CH₃)₂,
 (17) -O-CH(CH₃)CH₂N(CH₃)₂,
 (18) -O-CH₂CH₂ NH₂,
 5 (19) -O-CH(CH₃)CH₂NH₂,
 (20) -S-CH₃,
 (21) -C(O)CH₂C(O)C(O)OH,
 (22) -CH₂-CH(OH)-CH₂-O-R⁷, and
 (23) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);
- 10 R² is selected from:
- (1) -H,
 (2) -R³,
 (3) -CH₃,
 (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the
 15 hydrogen atoms on C₁₋₆ alkyl may be replaced with a
 fluorine atom,
 (5) -O-R⁶,
 (6) -S-R⁶,
 (7) -O-C₁₋₆ alkyl- SR⁶,
 20 (8) -C₁₋₆ alkyl (OR⁶)(R⁴),
 (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
 (10) -C₀₋₆ alkyl C(O)-R⁶,
 (11) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
 (12) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
 25 (13) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
 (14) -CH₂(OR⁷)-R⁶;

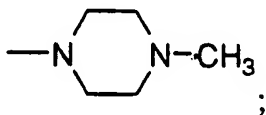
each R³ is independently selected from:

- (1) phenyl;
 (2) substituted phenyl with 1, 2, 3 or 4 substituents
 30 independently selected from:
 (a) halogen, selected from -F, -Cl, -Br,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,

- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,-, .
- (d) -CN,
- (e) hydroxy, and
- 5 (f) oxo;
- (3) thienyl,
- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from F, Cl, and Br,
- 10 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- (5) pyridyl,
- 15 (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 20 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) hydroxy, and
- (e) oxo;
- (7) imidazolyl,
- 25 (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
- 30 (b) -CH₃,
- (c) -CF₃,
- (d) -OCH₃,
- (e) -OCF₃, and
- (f) hydroxy;

- (11) C₃₋₆ cycloalkyl,
(12) substituted C₃₋₆ cycloalkyl with 1 or 2 substituents independently selected from:
- 5 (a) halogen, selected from -F, -Cl, and -Br,
(b) CH₃,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
10 (g) =O, and
(h) hydroxy;
- (13) piperidinyl,
(14) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- 15 (a) halogen selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
20 (f) =O, and
(g) hydroxy;
- (15) morpholinyl,
(16) substituted morpholinyl substituted on carbon or nitrogen with 1 or 2 substituents independently selected from:
- 25 (a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃, and
30 (f) hydroxy;
- (17) hexahydrothieno[3,4-d]imidazolyl,
(18) naphthyl,
(19) substituted naphthyl with 1, 2, or 3 substituents independently selected from:

- (a) -halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-,
 (d) -CF₃,
 5 (e) -OCF₃,
 (f) -CN, and
 (g) -hydroxy,
 (20) indolyl,
 (21) 1,2,3,4-tetrahydronaphthalenyl,
 10 (22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on
 carbon with a substituent selected from:
 (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-,
 15 (d) -CF₃,
 (e) -OCF₃,
 (f) -CN,
 (g) =O, and
 (h) hydroxy;
 20 (23) pyrazinyl;
 (24) substituted pyrazinyl substituted on nitrogen or carbon with
 one or two substituents independently selected from:
 (a) halogen, selected from -F, -Cl, and -Br,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 25 atoms may be replaced with a fluorine atom,
 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (d) hydroxy,
 (e) phenyloxy,
 30 (f) -C₀₋₆ alkyl-N(R⁷)₂, and
 (g)



- (25) pyrimidinyl;

- (26) substituted pyrimidinyl substituted on nitrogen or carbon with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) phenyl,
- (27) triazolyl;
- (28) substituted triazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (29) tetrazolyl;
- (30) substituted tetrazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (31) C3-6 cycloalkyl;
- (32) substituted C3-6 cycloalkyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (33) tetrahydrofuran;
- (34) substituted tetrahydrofuran substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (35) piperazinyl;

- (36) substituted piperazinyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl,
 - 5 (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) benzyl, and
 - (g) hydroxy;
- 10 (37) benzotriazolyl,
- (38) substituted benzotriazolyl substituted on carbon with one or two substituents independently selected from:
- (a) -halogen, selected from -F, -Cl. and -Br,
 - (b) -methyl,
 - 15 (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (39) benzoimidazolyl,
- 20 (40) substituted benzoimidazolyl substituted on carbon with one or two substituents independently selected from:
- (a) -halogen, selected from -F, -Cl. and -Br,
 - (b) -methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - 25 (e) -OCF₃,

each R⁴ is independently selected from:

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- 30 (4) -R³,
- (5) -C₁₋₃ alkyl-R³, and
- (6) -C(O)-R³;

each R⁵ is independently selected from:

- (1) -H,
- 35 (2) -C₁₋₃ alkyl,

- (3) $-\text{CF}_3$,
 (4) $-\text{R}^3$,
 (5) $-\text{C}_{1-3}$ alkyl- R^3 ,
 (6) $-\text{C}(\text{O})-\text{R}^3$,
 5 (7) $-\text{C}(\text{O})\text{OR}^4$, and
 (8) $-\text{C}(\text{O})\text{C}(\text{O})\text{OH}$;

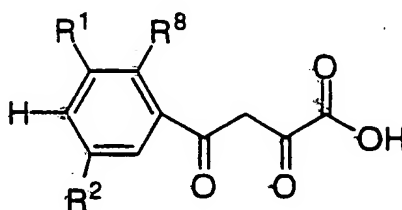
each R^6 is independently selected from:

- (1) $-\text{C}_{1-3}$ alkyl- R^3 , and
 (2) $-\text{R}^3$;
 10 each R^7 is independently selected from:
 (1) $-\text{H}$, and
 (2) $-\text{C}_{1-6}$ alkyl;

PROVIDED THAT:

- (1) at least one of R^1 and R^2 is not:
 15 (a) H ,
 (b) C_{1-6} alkyl, or
 (c) R^3 wherein R^3 is cycloalkyl; and
 (2) when R^2 is SR^6 , R^6 is R^3 .

- 20 7. The compound according to Claim 1 of structural formula:



and tautomers and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from:

- 25 (1) $-\text{H}$,
 (2) $-\text{CH}_3$,
 (3) $-\text{C}_{1-6}$ alkyl- OR^7 ;
 (4) $-\text{O}-\text{C}_{1-6}$ alkyl- OR^7 ,
 (5) $-\text{O}-\text{C}_{1-6}$ alkyl- SR^7 ,
 30 (6) $-\text{CF}_3$ or $-\text{CH}_2\text{CF}_3$,

- (7) -Cl,
- (8) -F,
- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -phenyl,
- 5 (11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- (a) -F, -Cl, or -Br,
- (b) CH₃,
- 10 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
- (d) -CF₃,
- (e) -SCH₃,
- (f) -CN,
- (g) hydroxy, and
- 15 (h) -C₀₋₆ alkyl-N(R⁷)₂,
- (12) -O-CH₂-phenyl, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- (a) -F, -Cl, or -Br,
- 20 (b) -CH₃,
- (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
- (d) -CF₃,
- (e) -SCH₃,
- (f) -CN,
- 25 (g) hydroxy, and
- (h) -C₀₋₆ alkyl-N(R⁷)₂,
- (13) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three fluorine atoms,
- (14) -C(O)CH₂C(O)C(O)OH,
- 30 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
- (16) -O-CH₂CH₂ N(CH₃)₂,
- (17) -O-CH(CH₃)CH₂N(CH₃)₂,
- (18) -O-CH₂CH₂ NH₂,
- (19) -O-CH(CH₃)CH₂NH₂,
- 35 (20) -S-CH₃,

- (21) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$,
 (22) $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}^7$, and
 (23) $-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}_2\text{N}(\text{R}^4)(\text{R}^5)$;

R^2 is selected from:

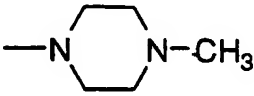
- 5 (1) $-\text{H}$,
 (2) $-\text{R}^3$,
 (3) $-\text{CH}_3$,
 (4) $-\text{C}_{1-6}$ alkyl substituted with R^3 , wherein one or more of the
 10 hydrogen atoms on C_{1-6} alkyl may be replaced with a
 fluorine atom,
 (5) $-\text{O}-\text{R}^6$,
 (6) $-\text{S}-\text{R}^6$,
 (7) $-\text{O}-\text{C}_{1-6}$ alkyl- SR^6 ;
 (8) $-\text{C}_{1-6}$ alkyl $(\text{OR}^6)(\text{R}^4)$,
 15 (9) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^4)(\text{R}^6)$,
 (10) $-\text{C}_{0-6}$ alkyl $\text{C}(\text{O})-\text{R}^6$,
 (11) $-\text{C}_{0-6}$ alkyl $\text{C}(\text{O})\text{CH}_2-\text{C}(\text{O})-\text{OH}$,
 (12) $-\text{C}_{1-6}$ alkyl $\text{NR}^4\text{C}(\text{O})-\text{R}^6$,
 (13) $-\text{C}_{1-6}$ alkyl- $\text{C}(\text{O})\text{N}(\text{R}^4)(\text{R}^5)$, and
 20 (14) $-\text{CH}_2(\text{OR}^7)-\text{R}^6$;

each R^3 is independently selected from:

- (1) phenyl,
 (2) substituted phenyl with 1, 2, 3 or 4 substituents
 independently selected from:
 25 (a) halogen, selected from $-\text{F}$, $-\text{Cl}$, $-\text{Br}$,
 (b) C_{1-6} alkyl, wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (c) C_{1-6} alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,-,
 30 (d) $-\text{CN}$,
 (e) hydroxy, and
 (f) oxo;
 (3) thienyl,

- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from F, Cl, and Br,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- (5) pyridyl,
- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) hydroxy, and
 - (e) oxo;
- (7) imidazolyl,
- (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) -CH₃,
 - (c) -CF₃,
 - (d) -OCH₃,
 - (e) -OCF₃, and
 - (f) hydroxy;
- (11) C₃₋₆ cycloalkyl,
- (12) substituted C₃₋₆ cycloalkyl with 1 or 2 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) CH₃,
 - (c) methyloxy-,
 - (d) -CF₃,

- (e) -OCF₃,
 - (f) -CN,
 - (g) =O, and
 - (h) hydroxy;
- 5 (13) piperidinyl,
- (14) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
- 10 (c) methoxy-,
- (d) -CF₃,
 - (e) -OCF₃,
 - (f) =O, and
 - (g) hydroxy;
- 15 (15) morpholinyl,
- (16) substituted morpholinyl substituted on carbon or nitrogen with 1 or 2 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
- 20 (c) methoxy-,
- (d) -CF₃,
 - (e) -OCF₃, and
 - (f) hydroxy;
- (17) hexahydrothieno[3,4-d]imidazolyl,
- 25 (18) naphthyl,
- (19) substituted naphthyl with 1, 2, or 3 substituents independently selected from:
- (a) -halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
- 30 (c) methoxy-,
- (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN, and
 - (g) -hydroxy,

- (20) indolyl,
- (21) 1,2,3,4-tetrahydronaphthalenyl,
- (22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on carbon with a substituent selected from:
- 5 (a) halogen, selected from -F, -Cl, and -Br,
- (b) methyl,
- (c) methoxy-,
- (d) -CF₃,
- (e) -OCF₃,
- 10 (f) -CN,
- (g) =O, and
- (h) hydroxy;
- (23) pyrazinyl;
- (24) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- 15 (a) halogen, selected from -F, -Cl, and -Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- 20 (d) hydroxy,
- (e) phenoxy,
- (f) -C₀₋₆ alkyl-N(R⁷)₂, and
- (g)
- 25  ;
- (25) pyrimidinyl;
- (26) substituted pyrimidinyl substituted on nitrogen or carbon with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
- 30 (b) methyl,
- (c) methoxy-, and
- (d) phenyl,
- (27) triazolyl;

- (28) substituted triazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (29) tetrazolyl;
- (30) substituted tetrazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (31) C₃₋₆ cycloalkyl;
- (32) substituted C₃₋₆ cycloalkyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (33) tetrahydrofuran;
- (34) substituted tetrahydrofuran substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (35) piperazinyl;
- (36) substituted piperazinyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,

- (f) benzyl, and
(g) hydroxy;
(37) benzotriazolyl,
(38) substituted benzotriazolyl substituted on carbon with one or
5 two substituents independently selected from:
(a) -halogen, selected from -F, -Cl. and -Br,
(b) -methyl,
(c) methoxy-,
(d) -CF₃, and
10 (e) -OCF₃,
(39) benzoimidazolyl, and
(40) substituted benzoimidazolyl substituted on carbon with one
or two substituents independently selected from:
(a) -halogen, selected from -F, -Cl. and -Br,
15 (b) -methyl,
(c) methoxy-,
(d) -CF₃, and
(e) -OCF₃;
each R⁴ is independently selected from:
20 (1) -H,
(2) -C₁₋₄ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₁₋₃ alkyl-R³, and
25 (6) -C(O)-R³;
each R⁵ is independently selected from:
(1) -H,
(2) -C₁₋₃ alkyl,
(3) -CF₃,
30 (4) -R³,
(5) -C₁₋₃ alkyl-R³,
(6) -C(O)-R³,
(7) -C(O)OR⁴, and
(8) -C(O)C(O)OH;
35 each R⁶ is independently selected from:

(1) -C₁₋₃ alkyl-R³, and

(2) -R³;

each R⁷ is independently selected from:

(1) -H, and

5 (2) -C₁₋₆ alkyl;

R⁸ is selected from methyl and -O- C₁₋₆ alkyl; and

PROVIDED THAT:

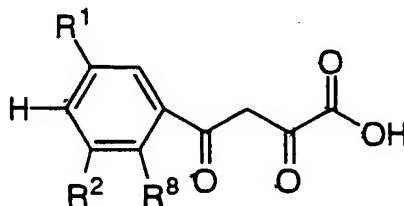
(1) at least one of R¹, R², and R⁸ is not:

(a) C₁₋₆ alkyl, or

10 (b) R³ wherein R³ is cycloalkyl; and

(2) when R² is SR⁶, R⁶ is R³.

8. The compound according to Claim 1 of structural formula:



and tautomers and pharmaceutically acceptable salts thereof, wherein:

R¹ is selected from:

(1) -H,

(2) -CH₃,

20 (3) -C₁₋₆ alkyl-OR⁷;

(4) -O-C₁₋₆ alkyl-OR⁷,

(5) -O-C₁₋₆ alkyl-SR⁷,

(6) -CF₃ or -CH₂CF₃,

(7) -Cl,

25 (8) -F,

(9) -C₀₋₃ alkyl-N(R⁴)(R⁵),

(10) -phenyl,

(11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:

30

- 5 (a) -F, -Cl, or -Br,
 (b) CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 (d) -CF₃,
 (e) -SCH₃,
 (f) -CN,
 (g) hydroxy,
 (h) -C₀₋₆ alkyl-N(R⁷)₂,
- 10 (12) -O-CH₂-phenyl, wherein the phenyl group may be
 unsubstituted or substituted with 1 to four substituents
 independently selected from:
 (a) -F, -Cl, or -Br,
 (b) CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 15 (d) -CF₃,
 (e) -SCH₃,
 (f) -CN,
 (g) hydroxy,
 (h) -C₀₋₆ alkyl-N(R⁷)₂,
- 20 (13) -O-C₁₋₆ alkyl, unsubstituted or substituted with one to three
 fluorine atoms,
 (14) -C(O)CH₂C(O)C(O)OH,
 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
 (16) -O-CH₂CH₂ N(CH₃)₂,
 25 (17) -O-CH(CH₃)CH₂N(CH₃)₂,
 (18) -O-CH₂CH₂ NH₂,
 (19) -O-CH(CH₃)CH₂NH₂,
 (20) -S-CH₃,
 (21) -C(O)CH₂C(O)C(O)OH,
 30 (22) -CH₂-CH(OH)-CH₂-O-R⁷, and
 (23) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

- (1) -H,
 (2) -R³,
 35 (3) -CH₃,

- (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the hydrogen atoms on C₁₋₆ alkyl may be replaced with a fluorine atom,
- (5) -O-R⁶,
- 5 (6) -S-R⁶,
- (7) -O-C₁₋₆ alkyl-SR⁶,
- (8) -C₁₋₆ alkyl-(OR⁶)(R⁴),
- (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (10) -C₀₋₆ alkyl-C(O)-R⁶,
- 10 (11) -C₀₋₆ alkyl-C(O)CH₂-C(O)-OH,
- (12) -C₁₋₆ alkyl-NR⁴C(O)-R⁶,
- (13) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (14) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- 15 (1) phenyl,
- (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, -Br,
- (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
- 20 atoms may be replaced with a fluorine atom,
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) -CN,
- (e) hydroxy, and
- 25 (f) oxo;
- (3) thienyl,
- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from F, Cl, and Br,
- 30 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- (5) pyridyl,

- 5
- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 - (d) hydroxy, and
 - (e) oxo;
- 10
- (7) imidazolyl,
- (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
- 15
- (a) halogen, selected from -F, -Cl, and -Br;
 - (b) -CH₃,
 - (c) -CF₃,
 - (d) -OCH₃,
 - (e) -OCF₃, and
 - (f) hydroxy;
- 20
- (11) C₃₋₆ cycloalkyl,
- (12) substituted C₃₋₆ cycloalkyl with 1 or 2 substituents independently selected from:
- 25
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) CH₃,
 - (c) methyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O, and
 - (h) hydroxy;
- 30
- (13) piperidinyl,
- (14) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
- 35
- (a) halogen selected from -F, -Cl, and -Br,

- (b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
5 (f) =O, and
(g) hydroxy;
(15) morpholinyl,
(16) substituted morpholinyl substituted at carbon or nitrogen
with 1 or 2 substituents independently selected from:
10 (a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃, and
15 (f) hydroxy;
(17) hexahydrothieno[3,4-d]imidazolyl,
(18) naphthyl,
(19) substituted naphthyl with 1, 2, or 3 substituents
independently selected from:
20 (a) -halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
(e) -OCF₃,
25 (f) -CN, and
(g) -hydroxy,
(20) indolyl, and
(21) 1,2,3,4-tetrahydronaphthalenyl,
(22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on
30 carbon with a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
(c) methoxy-,
(d) -CF₃,
35 (e) -OCF₃,

- (f) -CN,
 (g) =O, and
 (h) hydroxy;
- (23) pyrazinyl;
- 5 (24) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 10 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 (d) hydroxy,
 (e) phenyloxy,
 (f) -C₀₋₆ alkyl-N(R⁷)₂, and
 15 (g)
- *N1CCN(C)CC1
- (25) pyrimidinyl;
- (26) substituted pyrimidinyl substituted on nitrogen or carbon with a substituent selected from:
- 20 (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-, and
 (d) phenyl,
- (27) triazolyl;
- 25 (28) substituted triazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,
 (c) methoxy-, and
 (d) hydroxy,
- 30 (29) tetrazolyl;
- (30) substituted tetrazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 (b) methyl,

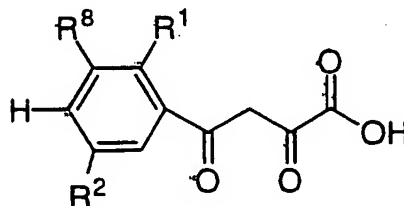
- (c) methoxy-, and
- (d) hydroxy,
- (31) C₃₋₆ cycloalkyl;
- (32) substituted C₃₋₆ cycloalkyl substituted with one or two
5 substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - 10 (e) -OCF₃,
- (33) tetrahydrofuran;
- (34) substituted tetrahydrofuran substituted with one or two
substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - 15 (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (35) piperazinyl;
- 20 (36) substituted piperazinyl substituted with one or two
substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - 25 (d) -CF₃,
 - (e) -OCF₃,
 - (f) benzyl, and
 - (g) hydroxy;
- (37) benzotriazolyl,
- 30 (38) substituted benzotriazolyl substituted on carbon with one or
two substituents independently selected from:
 - (a) -halogen, selected from -F, -Cl, and -Br,
 - (b) -methyl,
 - (c) methoxy-,
 - 35 (d) -CF₃, and

- (e) -OCF₃,
- (39) benzoimidazolyl, and
- (40) substituted benzoimidazolyl substituted on carbon with one or two substituents independently selected from:
- 5 (a) -halogen, selected from -F, -Cl. and -Br,
- (b) -methyl,
- (c) methoxy-,
- (d) -CF₃, and
- (e) -OCF₃;
- 10 each R⁴ is independently selected from:
- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- 15 (5) -C₁₋₃ alkyl-R³, and
- (6) -C(O)-R³;
- each R⁵ is independently selected from:
- (1) -H,
- (2) -C₁₋₃ alkyl,
- 20 (3) -CF₃,
- (4) -R³,
- (5) -C₁₋₃ alkyl-R³,
- (6) -C(O)-R³,
- (7) -C(O)OR⁴, and
- 25 (8) -C(O)C(O)OH;
- each R⁶ is independently selected from:
- (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;
- each R⁷ is independently selected from:
- 30 (1) -H, and
- (2) -C₁₋₆ alkyl;
- R⁸ is selected from methyl and -O- C₁₋₆ alkyl; and
- each n is independently selected from 0, 1 and 2;
- PROVIDED THAT:

- (1) at least one of R¹, R², and R⁸ is not:
 (a) C₁₋₆ alkyl, or
 (b) R³ wherein R³ is cycloalkyl; and
 (2) when R² is SR⁶, R⁶ is R³.

5

9. The compound according to Claim 1 of structural formula:



and tautomers and pharmaceutically acceptable salts thereof, wherein:

10 R¹ is selected from:

- (1) -H,
 (2) -CH₃,
 (3) -C₁₋₆ alkyl-OR⁷,
 (4) -O-C₁₋₆ alkyl-OR⁷,
 15 (5) -O-C₁₋₆ alkyl-SR⁷,
 (6) -CF₃ or -CH₂CF₃,
 (7) -Cl,
 (8) -F,
 (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
 20 (10) -phenyl,
 (11) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
 (a) -F, -Cl, or -Br,
 25 (b) CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 (d) -CF₃,
 (e) -SCH₃,
 (f) -CN,
 30 (g) hydroxy,

- (h) $-C_{0-6}$ alkyl- $N(R^7)_2$,
- (12) $-O-CH_2$ -phenyl, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- 5 (a) $-F$, $-Cl$, or $-Br$,
 (b) CH_3 ,
 (c) $-OCH_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-CF_3$,
 (e) $-SCH_3$,
- 10 (f) $-CN$,
 (g) hydroxy,
 (h) $-C_{0-6}$ alkyl- $N(R^7)_2$,
- (13) $-O-C_{1-6}$ alkyl, unsubstituted or substituted with one to three fluorine atoms, and
- 15 (14) $-C(O)CH_2C(O)C(O)OH$,
 (15) $-O-C_{1-6}$ alkyl- $NH-C(O)-OR^7$,
 (16) $-O-CH_2CH_2 N(CH_3)_2$,
 (17) $-O-CH(CH_3)CH_2N(CH_3)_2$,
 (18) $-O-CH_2CH_2 NH_2$,
- 20 (19) $-O-CH(CH_3)CH_2NH_2$,
 (20) $-S-CH_3$,
 (21) $-C(O)CH_2C(O)C(O)OH$,
 (22) $-CH_2-CH(OH)-CH_2-O-R^7$, and
 (23) $-C(OH)(CH_3)-CH_2N(R^4)(R^5)$;
- 25 R^2 is selected from:
- (1) $-H$,
 (2) $-R^3$,
 (3) $-CH_3$,
 (4) $-C_{1-6}$ alkyl substituted with R^3 , wherein one or more of the
- 30 hydrogen atoms on C_{1-6} alkyl may be replaced with a fluorine atom,
- (5) $-O-R^6$,
 (6) $-S-R^6$,
 (7) $-O-C_{1-6}$ alkyl- SR^6 ,

- (8) -C₁₋₆ alkyl (OR⁶)(R⁴),
- (9) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (10) -C₀₋₆ alkyl C(O)-R⁶,
- (11) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- 5 (12) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- (13) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (14) -CH₂(OR⁷)-R⁶;

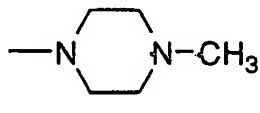
each R³ is independently selected from:

- (1) phenyl;
- 10 (2) substituted phenyl with 1, 2, 3 or 4 substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, -Br,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - 15 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,-,
 - (d) -CN,
 - (e) hydroxy, and
 - (f) oxo;
- 20 (3) thienyl,
- (4) substituted thienyl substituted on carbon with one or two substituents independently selected from:
 - (a) halogen, selected from F, Cl, and Br,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom, and
 - 25 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom;
- (5) pyridyl,
- (6) substituted pyridyl substituted on carbon with one or two substituents independently selected from:
 - 30 (a) halogen, selected from -F, -Cl, and -Br;
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,

- (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
- (d) hydroxy, and
- (e) oxo;
- 5 (7) imidazolyl,
- (8) pyrrolyl,
- (9) pyrazolyl
- (10) substituted pyrazolyl substituted on carbon with one or two substituents independently selected from:
 - 10 (a) halogen, selected from -F, -Cl, and -Br;
 - (b) -CH₃,
 - (c) -CF₃,
 - (d) -OCH₃,
 - (e) -OCF₃, and
 - 15 (f) hydroxy;
- (11) C₃₋₆ cycloalkyl,
- (12) substituted C₃₋₆ cycloalkyl with 1 or 2 substituents independently selected from:
 - 20 (a) halogen, selected from -F, -Cl, and -Br,
 - (b) CH₃,
 - (c) methyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - 25 (g) =O, and
 - (h) hydroxy;
- (13) piperidinyl,
- (14) substituted piperidinyl substituted on carbon with one or two substituents independently selected from:
 - 30 (a) halogen selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃,
 - (e) -OCF₃,

- (f) =O, and
- (g) hydroxy;
- (15) morpholinyl,
- (16) substituted morpholinyl substituted on carbon or nitrogen
5 with 1 or 2 substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃,
 - 10 (e) -OCF₃, and
 - (f) hydroxy;
- (17) hexahydrothieno[3,4-d]imidazolyl,
- (18) naphthyl,
- (19) substituted naphthyl with 1, 2, or 3 substituents
15 independently selected from:
 - (a) -halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃,
 - 20 (e) -OCF₃,
 - (f) -CN, and
 - (g) -hydroxy,
- (20) indolyl, and
- (21) 1,2,3,4-tetrahydronaphthalenyl,
- 25 (22) substituted 1,2,3,4-tetrahydronaphthalenyl substituted on
carbon with a substituent selected from:
 - (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - 30 (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O, and
 - (h) hydroxy;
 - 35 (23) pyrazinyl;

- (24) substituted pyrazinyl substituted on nitrogen or carbon with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) hydroxy,
 - (e) phenyloxy,
 - (f) -C₀₋₆ alkyl-N(R⁷)₂, and
 - (g)



- (25) pyrimidinyl;
- (26) substituted pyrimidinyl substituted on nitrogen or carbon with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) phenyl,
- (27) triazolyl;
- (28) substituted triazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (29) tetrazolyl;
- (30) substituted tetrazolyl with a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-, and
 - (d) hydroxy,
- (31) C₃₋₆ cycloalkyl;

- (32) substituted C₃₋₆ cycloalkyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (33) tetrahydrofuran;
- (34) substituted tetrahydrofuran substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (35) piperazinyl;
- (36) substituted piperazinyl substituted with one or two substituents independently selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) C₁₋₆ alkyl,
 - (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) benzyl, and
 - (g) hydroxy;
- (37) benzotriazolyl,
- (38) substituted benzotriazolyl substituted on carbon with one or two substituents independently selected from:
- (a) -halogen, selected from -F, -Cl, and -Br,
 - (b) -methyl,
 - (c) methoxy-,
 - (d) -CF₃, and
 - (e) -OCF₃,
- (39) benzoimidazolyl,

(40) substituted benzoimidazolyl substituted on carbon with one or two substituents independently selected from:

- (a) -halogen, selected from -F, -Cl. and -Br,
- (b) -methyl,
- 5 (c) methoxy-,
- (d) -CF₃, and
- (e) -OCF₃,

each R⁴ is independently selected from:

- (1) -H,
- 10 (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- (5) -C₁₋₃ alkyl-R³, and
- (6) -C(O)-R³;

15 each R⁵ is independently selected from:

- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) -CF₃,
- (4) -R³,
- 20 (5) -C₁₋₃ alkyl-R³,
- (6) -C(O)-R³,
- (7) -C(O)OR⁴, and
- (8) -C(O)C(O)OH;

each R⁶ is independently selected from:

- 25 (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

each R⁷ is independently selected from:

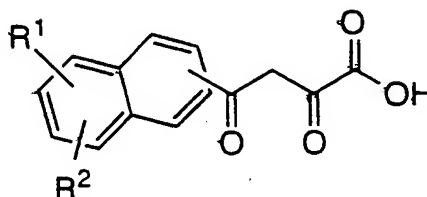
- (1) -H, and
- (2) -C₁₋₆ alkyl;

30 R⁸ is selected from methyl and -O- C₁₋₆ alkyl; and

PROVIDED THAT:

- (1) at least one of R¹, R², and R⁸ is not:
 - (b) C₁₋₆ alkyl, or
 - (c) R³ wherein R³ is cycloalkyl; and
- 35 (2) when R² is SR⁶, R⁶ is R³.

10. The compound according to Claim 1 of structural formula:



5 and tautomers and pharmaceutically acceptable salts thereof, wherein:
R¹ is selected from:

- (1) -H,
- (2) -CH₃,
- (3) -CH₂OCH₃,
- 10 (4) -OCH₂CH₂OH,
- (5) -OCH₂CH₂OCH₃,
- (6) -(CH₂)₆-OH,
- (7) -CF₃,
- (8) -F,
- 15 (9) -Cl,
- (10) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (11) -phenyl,
- (12) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:
 - (a) -F, -Cl, or -Br,
 - (b) CH₃,
 - (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 - (d) -CF₃,
 - 25 (e) -CN,
 - (f) hydroxy,
 - (g) -C₀₋₆ alkyl-N(R⁷)₂,
- (13) -O-CH₂-phenyl, wherein the phenyl group may be
unsubstituted or substituted with 1 to four substituents
independently selected from:
 - (a) -F, -Cl, or -Br,
 - (b) CH₃,
 - (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 - (d) -CF₃,
 - 30 (e) -CN,
 - (f) hydroxy,
 - (g) -C₀₋₆ alkyl-N(R⁷)₂,

- (a) -F, -Cl, or -Br,
 (b) -CH₃,
 (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 (d) -CF₃,
 5 (e) -CN,
 (f) hydroxy,
 (g) -C₀₋₆ alkyl-N(R⁷)₂, ,
 (14) -O-CH₃,
 (15) -OCH₂CH₃,
 10 (16) -OCH₂CF₃,
 (17) -OCF₃,
 (18) -OCH(CH₃)₂,
 (19) -C(O)CH₂C(O)C(O)OH,
 (20) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
 15 (21) -O-CH₂CH₂ N(CH₃)₂,
 (22) -O-CH(CH₃)CH₂N(CH₃)₂,
 (23) -O-CH₂CH₂NH₂,
 (24) -O-CH(CH₃)CH₂NH₂,
 (25) -S-CH₃,
 20 (26) -C(O)CH₂C(O)C(O)OH;
 (27) -CH₂-CH(OH)-CH₂-O-R⁷; and
 (28) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

- (1) -H,
 25 (2) -R³,
 (3) -CH₂-R³,
 (4) -CH₂CH₂-R³,
 (5) -CF₂-R³,
 (6) -CH(CH₃)-R³,
 30 (7) -O-R⁶,
 (8) -S-phenyl,
 (9) -C₁₋₆ alkyl (OR⁶)(R⁴) ,
 (10) -C₀₋₆ alkyl-N(R⁴)(R⁶) ,
 (11) -C(O)-R³,
 35 (12) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,

(13) $-C_{1-6}$ alkyl $NR^4C(O)R^6$,

(14) $-CH(OCH_3)R^3$, and

(15) $-CH(OH)R^3$;

each R^3 is independently selected from:

- 5 (1) phenyl;
- (2) substituted phenyl with 1, 2, or 3 substituents independently selected from:
- (a) halogen, selected from -F, -Cl, -Br,
- (b) $-CH_3$,
- 10 (c) methyloxy-,
- (d) ethyloxy-,
- (e) $-OCH_2CF_3$,
- (f) $-OCF_2CH_3$,
- (g) $-CF_3$,
- 15 (h) $-CH_2CF_3$,
- (i) $-CF_2CH_3$,
- (j) $-OCF_3$,
- (k) -CN, and
- (l) hydroxy;
- 20 (3) thienyl,
- (4) substituted thienyl substituted on a carbon atom with a substituent selected from:
- (a) F,
- (b) Cl, and
- 25 (c) methyl;
- (5) pyridyl,
- (6) substituted pyridyl substituted on a carbon with a substituent selected from:
- (a) -F,
- 30 (b) -Cl,
- (c) $-CH_3$,
- (d) $-CF_3$,
- (e) $-OCH_3$,
- (f) $-OCF_3$,

- (g) hydroxy, and
 (h) oxo;
- (7) pyrazolyl
 (8) substituted pyrazolyl substituted on carbon with one or two
 5 substituents independently selected from:
 (a) -F,
 (b) -Cl,
 (c) -CH₃, and
 (d) -CF₃;
- 10 (9) C₃₋₆ cycloalkyl,
 (10) piperidinyl,
 (11) substituted piperidinyl substituted on carbon with a
 substituent selected from:
 (a) methoxy-;
 15 (b) -OCF₃,
 (c) =O, and
 (d) hydroxy;
- (12) morpholinyl,
 (13) naphthyl,
 20 (14) 1,2,3,4-tetrahydronaphthalenyl,
 (15) pyrazinyl;
 (16) substituted pyrazinyl substituted on nitrogen or carbon with
 a substituent selected from:
 (a) halogen, selected from -F, -Cl, and -Br,
 25 (b) methyl,
 (c) -CF₃,
 (d) methoxy-,
 (e) -N(CH₃)₂, and
- The diagram shows a piperazine ring, which is a six-membered ring with two nitrogen atoms. One nitrogen atom is bonded to a substituent represented by a horizontal line (—N). The other nitrogen atom is bonded to a methyl group (N-CH₃).
- (f)
- 30 (17) pyrimidinyl,
 (18) [1,2,3]-triazolyl,
 (19) [1,2,4]-triazolyl,
 (20) tetrazolyl;

- (21) cyclopropyl,
(22) cyclobutyl,
(23) cyclopentyl,
(24) cyclohexyl,
5 (25) tetrahydrofuran,
(26) piperazinyl;
(27) substituted piperazinyl substituted with a substituent
selected from:
(a) -F,
10 (b) -Cl,
(c) methyl,
(d) -CF₃, and
(e) benzyl,
(28) benzotriazolyl,
15 (29) benzoimidazolyl,

each R⁴ is independently selected from:

- (1) -H,
(2) -C₁₋₄ alkyl,
(3) -CF₃,
20 (4) -R³,
(5) -C₁₋₃ alkyl-R³, and
(6) -C(O)-R³;

each R⁵ is independently selected from:

- (1) -H,
25 (2) -CH₃,
(3) -CF₃,
(4) phenyl,
(5) -benzyl,
(6) -C(O)OR⁴, and
30 (7) -C(O)C(O)OH;

each R⁶ is independently selected from:

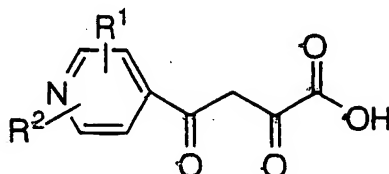
- (1) -C₁₋₃ alkyl-R³, and
(2) -R³;

each R⁷ is independently selected from:

- 35 (1) -H, and

(2) -C₁₋₆ alkyl.

11. The compound according to Claim 1 of structural formula:



5

and tautomers and pharmaceutically acceptable salts thereof, wherein:
R¹ is selected from:

- (1) -H,
- (2) -CH₃,
- 10 (3) -CH₂OCH₃,
- (4) -OCH₂CH₂OH,
- (5) -OCH₂CH₂OCH₃,
- (6) -(CH₂)₆-OH,
- (7) -CF₃,
- 15 (8) -F,
- (9) -Cl,
- (10) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (11) -phenyl,
- (12) phenyl C₁₋₃ alkyl-, wherein the phenyl group may be
- 20 unsubstituted or substituted with 1 to four substituents independently selected from:
- (a) -F, -Cl, or -Br,
- (b) CH₃,
- (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
- 25 (d) -CF₃,
- (e) -CN,
- (f) hydroxy,
- (g) -C₀₋₆ alkyl-N(R⁷)₂,

- (13) -O-CH₂-phenyl, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
- (a) -F, -Cl, or -Br,
 - (b) CH₃,
 - (c) -OCH₃, OCH₂CH₃, OCF₃, or OCH₂CF₃,
 - (d) -CF₃,
 - (e) -CN,
 - (f) hydroxy,
 - (g) -C₀₋₆ alkyl-N(R⁷)₂,
- (14) -O-CH₃,
- (15) -OCH₂CH₃,
- (16) -OCH₂CF₃,
- (17) -OCF₃,
- (18) -OCH(CH₃)₂,
- (19) -C(O)CH₂C(O)C(O)OH,
- (20) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
- (21) -O-CH₂CH₂N(CH₃)₂,
- (22) -O-CH(CH₃)CH₂N(CH₃)₂,
- (23) -O-CH₂CH₂NH₂,
- (24) -O-CH(CH₃)CH₂NH₂,
- (25) -S-CH₃,
- (26) -C(O)CH₂C(O)C(O)OH;
- (27) -CH₂-CH(OH)-CH₂-O-R⁷; and
- (28) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

R² is selected from:

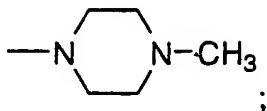
- (1) -H,
- (2) -R³,
- (3) -CH₂-R³,
- (4) -CH₂CH₂-R³,
- (5) -CF₂-R³,
- (6) -CH(CH₃)-R³,
- (7) -O-R⁶,
- (8) -S -phenyl,

- 5
- (9) -C₁₋₆ alkyl (OR⁶)(R⁴) ,
 - (10) -C₀₋₆ alkyl-N(R⁴)(R⁶) ,
 - (11) -C(O)-R³,
 - (12) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
 - (13) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
 - (14) -CH(OCH₃)R³, and
 - (15) -CH(OH)R³;

each R³ is independently selected from:

- (1) phenyl;
- 10 (2) substituted phenyl with 1, 2, or 3 substituents independently selected from:
 - (a) halogen, selected from -F, -Cl, -Br,
 - (b) -CH₃,
 - (c) methyloxy-,
 - 15 (d) ethyloxy-,
 - (e) -OCH₂CF₃,
 - (f) -OCF₂CH₃,
 - (g) -CF₃,
 - (h) -CH₂CF₃,
 - 20 (i) -CF₂CH₃,
 - (j) -OCF₃,
 - (k) -CN, and
 - (l) hydroxy;
- (3) thienyl,
- 25 (4) substituted thienyl substituted on a carbon atom with a substituent selected from:
 - (a) F,
 - (b) Cl, and
 - (c) methyl;
- 30 (5) pyridyl,
- (6) substituted pyridyl substituted on a carbon with a substituent selected from:
 - (a) -F,
 - (b) -Cl,

- (c) -CH₃,
(d) -CF₃,
(e) -OCH₃,
(f) -OCF₃,
5 (g) hydroxy, and
(h) oxo;
(7) pyrazolyl
(8) substituted pyrazolyl substituted on carbon with one or two
substituents independently selected from:
10 (a) -F,
(b) -Cl,
(c) -CH₃, and
(d) -CF₃;
(9) C₃₋₆ cycloalkyl,
15 (10) piperidinyl,
(11) substituted piperidinyl substituted on carbon with a
substituent selected from:
(a) methoxy-,
(b) -OCF₃,
20 (c) =O, and
(d) hydroxy;
(12) morpholinyl,
(13) naphthyl,
(14) 1,2,3,4-tetrahydronaphthalenyl,
25 (15) pyrazinyl;
(16) substituted pyrazinyl substituted on nitrogen or carbon with
a substituent selected from:
(a) halogen, selected from -F, -Cl, and -Br,
(b) methyl,
30 (c) -CF₃,
(d) methoxy-,
(e) -N(CH₃)₂, and
(f)



- (17) pyrimidinyl,
 (18) [1,2,3]-triazolyl,
 (19) [1,2,4]-triazolyl,
 5 (20) tetrazolyl;
 (21) cyclopropyl,
 (22) cyclobutyl,
 (23) cyclopentyl,
 (24) cyclohexyl,
 10 (25) tetrahydrofuran,
 (26) piperazinyl;
 (27) substituted piperazinyl substituted with a substituent
 selected from:
 (a) -F,
 15 (b) -Cl,
 (c) methyl,
 (d) -CF₃, and
 (e) benzyl,
 (28) benzotriazolyl,
 20 (29) benzoimidazolyl,
 each R⁴ is independently selected from:
 (1) -H,
 (2) -C₁₋₄ alkyl,
 (3) -CF₃,
 25 (4) -R³,
 (5) -C₁₋₃ alkyl-R³, and
 (6) -C(O)-R³;
 each R⁵ is independently selected from:
 30 (1) -H,
 (2) -CH₃,
 (3) -CF₃,
 (4) phenyl,
 (5) -benzyl,

(6) $-\text{C}(\text{O})\text{OR}^4$, and

(7) $-\text{C}(\text{O})\text{C}(\text{O})\text{OH}$;

each R^6 is independently selected from:

(1) $-\text{C}_{1-3}$ alkyl- R^3 , and

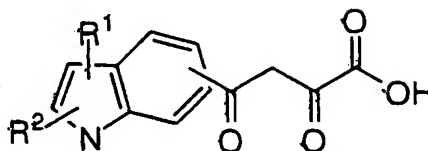
5 (2) $-\text{R}^3$;

each R^7 is independently selected from:

(1) $-\text{H}$, and

(2) $-\text{C}_{1-6}$ alkyl.

10 12. The compound according to Claim 1 of structural formula:



and tautomers and pharmaceutically acceptable salts thereof, wherein:

R^1 is selected from:

15 (1) $-\text{H}$,

(2) $-\text{CH}_3$,

(3) $-\text{CH}_2\text{OCH}_3$,

(4) $-\text{OCH}_2\text{CH}_2\text{OH}$,

(5) $-\text{OCH}_2\text{CH}_2\text{OCH}_3$,

20 (6) $-(\text{CH}_2)_6-\text{OH}$,

(7) $-\text{CF}_3$,

(8) $-\text{F}$,

(9) $-\text{Cl}$,

(10) $-\text{C}_{0-3}$ alkyl- $\text{N}(\text{R}^4)(\text{R}^5)$,

25 (11) $-\text{phenyl}$,

(12) phenyl C_{1-3} alkyl-, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:

(a) $-\text{F}$, $-\text{Cl}$, or $-\text{Br}$,

30 (b) $-\text{CH}_3$,

(c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,

- (d) $-\text{CF}_3$,
 (e) $-\text{CN}$,
 (f) hydroxy,
 (g) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^7)_2$,
- 5 (13) $-\text{O}-\text{CH}_2$ -phenyl, wherein the phenyl group may be unsubstituted or substituted with 1 to four substituents independently selected from:
 (a) $-\text{F}$, $-\text{Cl}$, or $-\text{Br}$,
 (b) CH_3 ,
 10 (c) $-\text{OCH}_3$, OCH_2CH_3 , OCF_3 , or OCH_2CF_3 ,
 (d) $-\text{CF}_3$,
 (e) $-\text{CN}$,
 (f) hydroxy,
 (g) $-\text{C}_{0-6}$ alkyl- $\text{N}(\text{R}^7)_2$,
- 15 (14) $-\text{O}-\text{CH}_3$,
 (15) $-\text{OCH}_2\text{CH}_3$,
 (16) $-\text{OCH}_2\text{CF}_3$,
 (17) $-\text{OCF}_3$,
 (18) $-\text{OCH}(\text{CH}_3)_2$,
 20 (19) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$,
 (20) $-\text{O}-\text{C}_{1-6}$ alkyl- $\text{NH}-\text{C}(\text{O})-\text{OR}^7$,
 (21) $-\text{O}-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$,
 (22) $-\text{O}-\text{CH}(\text{CH}_3)\text{CH}_2\text{N}(\text{CH}_3)_2$,
 (23) $-\text{O}-\text{CH}_2\text{CH}_2\text{NH}_2$,
 25 (24) $-\text{O}-\text{CH}(\text{CH}_3)\text{CH}_2\text{NH}_2$,
 (25) $-\text{S}-\text{CH}_3$,
 (26) $-\text{C}(\text{O})\text{CH}_2\text{C}(\text{O})\text{C}(\text{O})\text{OH}$;
 (27) $-\text{CH}_2-\text{CH}(\text{OH})-\text{CH}_2-\text{O}-\text{R}^7$; and
 (28) $-\text{C}(\text{OH})(\text{CH}_3)-\text{CH}_2\text{N}(\text{R}^4)(\text{R}^5)$;
- 30 R^2 is selected from:
 (1) $-\text{H}$,
 (2) $-\text{R}^3$,
 (3) $-\text{CH}_2-\text{R}^3$,
 (4) $-\text{CH}_2\text{CH}_2-\text{R}^3$,

- (5) -CF₂-R³,
- (6) -CH(CH₃)-R³,
- (7) -O-R⁶,
- (8) -S-phenyl,
- 5 (9) -C₁₋₆ alkyl (OR⁶)(R⁴) ,
- (10) -C₀₋₆ alkyl-N(R⁴)(R⁶) ,
- (11) -C(O)-R³,
- (12) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- (13) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- 10 (14) -CH(OCH₃)R³, and
- (15) -CH(OH)R³;

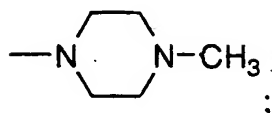
each R³ is independently selected from:

- (1) phenyl;
- (2) substituted phenyl with 1, 2, or 3 substituents independently
 - 15 selected from:
 - (a) halogen, selected from -F, -Cl, -Br,
 - (b) -CH₃,
 - (c) methyloxy-,
 - (d) ethyloxy-,
 - 20 (e) -OCH₂CF₃,
 - (f) -OCF₂CH₃,
 - (g) -CF₃,
 - (h) -CH₂CF₃,
 - (i) -CF₂CH₃,
 - 25 (j) -OCF₃,
 - (k) -CN, and
 - (l) hydroxy;
 - (3) thienyl,
 - (4) substituted thienyl substituted on a carbon atom with a
 - 30 substituent selected from:
 - (a) F,
 - (b) Cl, and
 - (c) methyl;
 - (5) pyridyl,

- (6) substituted pyridyl substituted on a carbon with a
substituent selected from:
- (a) -F,
 - (b) -Cl,
 - (c) -CH₃,
 - (d) -CF₃,
 - (e) -OCH₃,
 - (f) -OCF₃,
 - (g) hydroxy, and
 - (h) oxo;
- (7) pyrazolyl
- (8) substituted pyrazolyl substituted on carbon with one or two
substituents independently selected from:
- (a) -F,
 - (b) -Cl,
 - (c) -CH₃, and
 - (d) -CF₃;
- (9) C₃-6 cycloalkyl,
- (10) piperidinyl,
- (11) substituted piperidinyl substituted on carbon with a
substituent selected from:
- (a) methoxy-,
 - (b) -OCF₃,
 - (c) =O, and
 - (d) hydroxy;
- (12) morpholinyl,
- (13) naphthyl,
- (14) 1,2,3,4-tetrahydronaphthalenyl,
- (15) pyrazinyl;
- (16) substituted pyrazinyl substituted on nitrogen or carbon with
a substituent selected from:
- (a) halogen, selected from -F, -Cl, and -Br,
 - (b) methyl,
 - (c) -CF₃,
 - (d) methoxy-,

(e) $-\text{N}(\text{CH}_3)_2$, and

(f)



- (17) pyrimidinyl,
 5 (18) [1,2,3]-triazolyl,
 (19) [1,2,4]-triazolyl,
 (20) tetrazolyl;
 (21) cyclopropyl,
 (22) cyclobutyl,
 10 (23) cyclopentyl,
 (24) cyclohexyl,
 (25) tetrahydrofuran,
 (26) piperazinyl;
 (27) substituted piperazinyl substituted with a substituent
 15 selected from:
 (a) $-\text{F}$,
 (b) $-\text{Cl}$,
 (c) methyl,
 (d) $-\text{CF}_3$, and
 20 (e) benzyl,
 (28) benzotriazolyl,
 (29) benzoimidazolyl,

each R^4 is independently selected from:

- (1) $-\text{H}$,
 25 (2) $-\text{C}_{1-4}$ alkyl,
 (3) $-\text{CF}_3$,
 (4) $-\text{R}^3$,
 (5) $-\text{C}_{1-3}$ alkyl- R^3 , and
 (6) $-\text{C}(\text{O})-\text{R}^3$;

30 each R^5 is independently selected from:

- (1) $-\text{H}$,
 (2) $-\text{CH}_3$,
 (3) $-\text{CF}_3$,

- (4) phenyl,
- (5) -benzyl,
- (6) -C(O)OR⁴, and
- (7) -C(O)C(O)OH;

5 each R⁶ is independently selected from:

- (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

each R⁷ is independently selected from:

- (1) -H, and
- 10 (2) -C₁₋₆ alkyl.

13. A compound according to Claim 1, selected from:

- (1) 3-biphenyl-4-yl-2,4-dioxobutanoic acid,
- (2) 4-(3,5-bis-benzyloxyphenyl)-2-hydroxy-4-oxo-but-2-enoic acid,
- 15 (3) 4-[3-(3,4-difluorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (4) 4-[3-(4-methylbenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (5) 4-(3-benzyloxy-5-methoxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- 20 (6) 4-(3-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (7) 4-[3-(4-chlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (8) 4-[3-(3,4-dichlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- 25 (9) 4-[3-(4-fluorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (10) 4-[3-(3-chlorobenzyl)oxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- 30 (11) 4-[3-benzyloxy-5-(6-*tert*-butoxycarbonylamino-hexyloxy)phenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (12) 4-(3-(4-methoxybenzyloxy)phenyl)-4-oxo-2-butenic acid,
- (13) 4-(3-benzyloxy-5-hydroxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- 35 (14) 4-(3-(1-phenylethoxy)phenyl)-4-oxo-2-butenic acid,

- (15) 4-[3-benzyloxy-5-(6-[5-(2-oxohexahydrothieno[3,4-*d*]imidazol-4-yl)pentanoylamino]hexyloxy)-phenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- 5 (16) 4-[3-(6-aminohexyloxy)-5-benzyloxyphenyl]-2-hydroxy-4-oxobut-2-enoic acid,
- (17) 4-(3-dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (18) 4-(3-chloro-phenyl)-2,4-dioxobutanoic acid, and
- (19) 4-(3-benzyl-phenyl)-2,4-dioxo-butanoic acid,
- (20) 4-(4-dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- 10 (21) 4-(4-benzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (22) 4-(2-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (23) 4-naphthalen-1-yl-2,4-dioxobutanoic acid,
- (24) 4-naphthalen-2-yl-2,4-dioxobutanoic acid,
- (25) 4-(6-benzyloxy-2-oxo-1,2-dihydropyridin-4-yl)-2-hydroxy-4-oxobut-2-enoic acid,
- 15 (26) 4-(2,6-Bis benzyloxypyridin-4-yl)-2,4-dioxobutanoic acid,
- (27) 4-[1-(4-fluorobenzyl)-5-indolyl]-2-hydroxy-4-oxo-2-butenic acid,
- (28) 4-[1-(4-fluorobenzyl)-4-indolyl]-2-hydroxy-4-oxo-2-butenic acid,
- 20 (29) 4-(4-benzyloxyphenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (30) 4-[1-(4-fluorobenzyl)-6-indolyl]-2-hydroxy-4-oxo-2-butenic acid, and
- (31) 4-biphenyl-4-yl-2,4-dioxobutanoic acid,
- 25 and tautomers and pharmaceutically acceptable salts thereof.

14. A compound selected from the group consisting of:

- (1) 4-(3,5-Bis-benzyloxy-phenyl)-2,4-dioxobutanoic acid,
- (2) 4-[3-Benzyloxy-5-(2-morpholin-4-yl-ethoxy)-phenyl]-2,4-dioxobutanoic acid,
- 30 (3) 4-[3-Benzyloxy-5-(6-*tert*-butoxycarbonylamino-hexyloxy)-phenyl]-2,4-dioxobutanoic acid,
- (4) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,
- (5) 4-[3-(2-chlorobenzyl)phenyl]-2,4-dioxobutanoic acid,
- 35 (6) 4-(4-Dibenzylaminophenyl)-2,4-dioxobutanoic acid,

- (7) 4-(3-Dibenzylaminophenyl)-2,4-dioxobutanoic acid,
(8) 1-(3-benzyloxy-5-methoxyphenyl)-2,4-dioxobutanoic acid,
(9) 1-(3-Benzyloxyphenyl)-2,4-dioxobutanoic acid,
(10) 1-(2-Benzyloxyphenyl)-2,4-dioxobutanoic acid,
5 (11) 1-[3-(4-Fluorobenzyloxy)phenyl]-2,4-dioxobutanoic acid,
(12) 1-[3-(3,4-Difluorobenzyloxy)phenyl]-2,4-dioxobutanoic acid,
(13) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-
butyric acid,
(14) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-
10 butyric acid,
(15) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
(16) 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-
phenyl]butyric acid,
(17) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
15 (18) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
(19) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-
butyric acid,
(20) 4-[5-Benzyl-2-isopropoxyphenyl]-2,4-dioxobutyric acid,
(21) 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-
20 dioxobutyric acid,
(22) 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid,
(23) 4-[5-Benzyl-2-isopropoxy-3-methoxyphenyl]-2,4-dioxo-butyric
acid,
(24) 4-[5-Benzyl-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid,
25 (25) 4-[5-Benzyl-3-dimethylamino-2-methoxyphenyl]-2,4-
dioxobutyric acid,
(26) 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-
butyric acid,
(27) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric
30 acid,
(28) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-
dioxobutyric acid,
(29) 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric
acid,

- (30) 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (31) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid,
- 5 (32) 4-(3-Benzyl-4-methoxyphenyl)-2,4-dioxobutyric acid,
- (33) 4-(5-Benzyl-2-methoxyphenyl)-2,4-dioxobutyric acid,
- (34) 4-(3-Benzyl-4-fluorophenyl)-2,4-dioxobutyric acid,
- (35) 4-(3-Benzyl-4-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid,
- 10 (36) 4-[5-(2-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid,
- (37) 2,4-Dioxo-4-(3-pyridin-2-ylmethylphenyl)butyric acid,
- (38) 4-(5-Benzyl-3-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid,
- 15 (39) 4-(5-Benzyl-3-methoxyphenyl)-2,4-dioxobutyric acid,
- (40) 4-(5-Benzyl-2-benzyloxy-3-methoxyphenyl)-2,4-dioxobutyric acid,
- (41) 4-[5-(3-Methylbenzyl)-2,3-dimethoxyphenyl]-2,4-dioxobutyric acid,
- 20 (42) 4-(5-Benzyl-3-benzyloxyphenyl)-2,4-dioxobutyric acid,
- (43) 4-[5-Benzyl-2-(2-hydroxy)ethoxyphenyl]-2,4-dioxo-2-butanoic acid,
- (44) 2,4-Dioxo-4-(3-pyridin-3-ylmethylphenyl)butyric acid,
- (45) 4-[3-(3-Methyl-pyridin-2-ylmethyl)phenyl]-2,4-dioxo-butyric acid,
- 25 (46) 4-(5-Benzyl-2-methylsulfanylphenyl)-2,4-dioxobutyric acid,
- (47) 4-(5-Benzyl-3-N-morpholinophenyl)-2,4-dioxobutyric acid,
- (48) 4-(8-Benzyl-4-methyl-3,4-dihydro-2h-benzo[1,4]oxazin-6-yl)-2,4-dioxobutyric acid,
- 30 (49) 4-[5-(2-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid,
- (50) 4-[5-(3-Chlorobenzyl)-3-N,N-dimethylaminophenyl]-2,4-dioxobutyric acid,
- (51) 4-(5-Benzyl-2,3,4-trimethoxyphenyl)-2,4-dioxobutyric acid,
- 35 (52) 4-(6-Benzylbenzo[1,3]dioxol-4-yl)-2,4-dioxobutyric acid,

- (53) 4-[3-Benzyl-5-(morpholine-4-carbonyl)phenyl]-2,4-dioxobutyric acid,
- (54) 4-(3-Benzyl-5-pyridine-2-ylmethylphenyl)-2,4-dioxobutyric acid,
- 5 (55) 4-[3-Benzyl-5-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid,
- (56) 4-(3-Benzyl-5-pyridine-3-ylmethylphenyl)-2,4-dioxobutyric acid,
- (57) 4-[3-Benzyl-5-(2-dimethylamino-1-hydroxy-1-methylethyl)phenyl]-2,4-dioxobutyric acid,
- 10 (58) 4-(5-Benzyl-2-N,N-dimethylaminophenyl)-2,4-dioxobutyric acid,
- (59) 4-(5-Benzyl-2-fluorophenyl)-2,4-dioxobutyric acid,
- (60) 4-(5-Benzyl-3-hydroxymethyl-2-methoxyphenyl)-2,4-dioxobutyric acid,
- 15 (61) 4-[5-Benzyl-2-(pyrazin-2-yloxy)phenyl]-2,4-dioxobutyric acid,
- (62) 4-[3-Benzyl-5-(2-oxopiperidin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid,
- (63) 4-[5-Benzyl-2-methoxy-3-(morpholinomethyl)phenyl]-2,4-dioxobutyric acid,
- 20 (64) 4-[3-(2-Chlorobenzyl)-5-pyridin-2-ylmethylphenyl]-2,4-dioxobutyric acid,
- (65) 4-[5-Benzyl-2-methoxy-3-(4-methylpiperazin-1-ylmethyl)phenyl]-2,4-dioxobutyric acid,
- 25 (66) 4-(5-Benzyl-2-methoxymethylphenyl)-2,4-dioxobutyric acid,
- (67) 4-[3-(2-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- (68) 4-[3-(4-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- 30 (69) 4-[3-(3-Fluorobenzyl)-5-morpholinomethylphenyl]-2,4-dioxobutyric acid,
- (70) 4-[5-Benzyl-2-methoxy-3-(tert-butylcarbonyl)phenyl]-2,4-dioxobutyric acid,
- (71) 4-(3-Benzyl-5-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- 35

- (72) 4-[5-Benzyl-3-(N'-methyl-N-piperazinyl)phenyl]-2,4-dioxobutyric acid,
- (73) 4-(3-Benzyl-5-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- 5 (74) 4-(6-Benzyl-3-oxo-3,4-dihydro-2-H-benzo[1,4]oxazin-8-yl)-2,4-dioxobutyric acid,
- (75) 4-[5-Benzyl-2-(pyrimidin-2-yloxy)phenyl]-2,4-dioxobutyric acid,
- (76) 4-(5-Benzyl-3-amino-2-methoxyphenyl)-2,4-dioxobutyric acid,
- 10 (77) 4-(5-Benzyl-2-ethoxyphenyl)-2,4-dioxobutyric acid,
- (78) 4-[5-Benzyl-2-(2-morpholin-4-yl-ethoxy)phenyl]-2,4-dioxobutyric acid,
- (79) 4-(5-Benzyl-2-trifluoroethoxyphenyl)-2,4-dioxobutyric acid,
- 15 (80) 4-(5-Benzyl-2-cyclobutylloxyphenyl)-2,4-dioxobutyric acid,
- (81) 4-(5-Benzyl-2-cyclopentylloxyphenyl)-2,4-dioxobutyric acid,
- (82) 4-(3-Benzyl-5-tetrazol-2-ylmethylphenyl)-2,4-dioxobutyric acid,
- (83) 4-(5-Benzyl-2,3-diisopropoxyphenyl)-2,4-dioxobutyric acid,
- 20 (84) 4-(5-Benzyl-2-isopropoxy-3-N-methylaminophenyl)-2,4-dioxobutyric acid,
- (85) 4-(5-Benzyl-2-isopropoxy-3-N,N-dimethylaminophenyl)-2,4-dioxo-butyric acid,
- (86) 4-[5-Benzyl-2-isopropoxy-3-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-dioxobutyric acid,
- 25 (87) 4-[5-Benzyl-2-isopropoxy-3-(morpholinomethyl)phenyl]-2,4-dioxo-butyric acid,
- (88) 4-(5-Benzyl-2-isopropoxy-3-N,N-dimethylaminomethylphenyl)-2,4-dioxo-butyric acid,
- 30 (89) 4-(7-Benzylbenzo[1,3]dioxol-5-yl)-2-hydroxy-4-oxobut-2-enoic acid,
- (90) 2-Hydroxy-4-oxo-4-(3-phenylindan-5-yl)but-2-enoic acid,
- (91) 4-(Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,
- (92) 3-(3-Benzyl-5-carboxyacetylphenyl)-3-oxopropionic acid,
- 35 (93) 4-(4-Dibenzylaminophenyl)-2-hydroxy-4-oxobut-2-enoic acid,

- (94) 4-(5-Benzyl-3-methoxy-2-methylthioethoxyphenyl)-2,4-dioxobutyric acid,
- (95) 4-(7-Benzyl-2,3-dihydrobenzo[1,4]dioxin-5-yl)-2,4-dioxobutyric acid,
- 5 (96) (+/-) 4-(8-Benzyl-3-hydroxy-3,4-dihydro-2H-benzo[B][1,4]dioxepin-6-yl)-2,4-dioxobutyric acid,
- (97) 4-(2,3-Dimethoxy-5-pent-4-enylphenyl)-2,4-dioxobutyric acid,
- (98) 4-(5-Cyclopropylmethyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
- 10 (99) (6-Benzyl-1-oxo-indan-2-ylidene)-hydroxyacetic acid,
- (100) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (101) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- 15 (102) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-dioxobutyric acid,
- (103) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (104) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (105) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-butyric acid,
- 20 (106) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyric acid,
- (107) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyric acid,
- 25 (108) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyric acid,
- (109) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (110) 4-[1-(2,6-Difluorobenzyl)-1H-indol-6-yl]-2,4-dioxobutyric acid,
- 30 (111) 4-(1-Benzyl-1H-indol-6-yl)-2,4-dioxobutyric acid,
- (112) 1-[1-(4-Fluorobenzyl)-6-indolyl]-2,4-dioxobutanoic acid,
- (113) 1-[1-(4-Fluorobenzyl)-4-indolyl]-2,4-dioxobutanoic acid,
- (114) 4-[3-(2,4-difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
- (115) 2,4-dioxo-4-[3-(2,6-difluoro-benzyl)-phenyl]-butyric acid,
- 35 (116) 2,4-dioxo-4-[3-(2,4,6-trifluoro-benzyl)-phenyl]-butyric acid,

- (117) 2,4-dioxo-4-[3-(2-fluoro-3-chloro-benzyl)-phenyl]-butyric acid,
(118) 2,4-dioxo-4-[3-(2-methyl-4-fluoro-benzyl)-phenyl]-butyric acid,
(119) 4-[3-(2,3-dichloro-benzyl)-phenyl]-2,4-dioxo-butylric acid,
5 (120) 4-[3-(2-chloro-3-methylbenzyl)phenyl]-2,4-dioxobutyric acid,
(121) 2,4-dioxo-4-[3-(2,6-dichloro-benzyl)-phenyl]-butyric acid,
(122) 2,4-dioxo-4-[3-(2,3,4,5,6-penta-fluoro-benzyl)-phenyl]-butyric acid,
(123) 4-[3-(2-fluorobenzyl)phenyl]-2,4-dioxobutyric acid,
10 (124) 2,4-dioxo-4-[3-(2-chloro-4-fluoro-benzyl)-phenyl]-butyric acid,
(125) 4-[3-(2-methylbenzyl)phenyl]-2,4-dioxobutyric acid,
(126) 2,4-dioxo-4-[3-(2-methoxybenzyl)phenyl]butyric acid,
(127) 4-[3-(2-chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
(128) 4-[3-(2-bromobenzyl)phenyl]-2,4-dioxobutyric acid,
15 (129) 4-[5-(4-fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-butylric acid,
(130) 4-[3-(3-chloro-2-methyl-benzyl)phenyl]-2,4-dioxobutyric acid,
(131) 4-[3-(2,3-difluoro-benzyl)-phenyl]-2,4-dioxo-butylric acid,
(132) 4-(3,5-dibenzylphenyl)-2,4-dioxo-butylric acid,
20 (133) 2,4-dioxo-4-[3-(2-trifluoromethylbenzyl)phenyl]butyric acid,
(134) 4-[3-(4-fluorobenzyl)phenyl]-2,4-dioxobutyric acid,
(135) 4-[3-(3-chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
(136) 2,4-dioxo-4-[3-(2-bromo-3-chloro-benzyl)-phenyl]-butyric acid,
25 (137) 4-(3-benzylphenyl)-2,4-dioxo-butylric acid,
(138) 4-[3-(2-fluoro-3-methyl-benzyl)-phenyl]-2,4-dioxo-butylric acid,
(139) 4-[3-(3-chloro-4-fluoro-benzyl)-phenyl]-2,4-dioxo-butylric acid,
(140) 2,4-dioxo-4-[3-(2-bromo-4-fluoro-benzyl)-phenyl]-butyric acid,
30 (141) 4-[3-(3-bromobenzyl)phenyl]-2,4-dioxobutyric acid,
(142) 4-[3-(2,5-difluoro-benzyl)-phenyl]-2,4-dioxo-butylric acid,
(143) 4-[3-(5-chloro-2-fluoro-benzyl)phenyl]-2,4-dioxobutyric acid,
(144) 4-[3-(3-methylbenzyl)phenyl]-2,4-dioxobutyric acid,
(145) 4-(3-benzyl-4-methyl-phenyl)-2,4-dioxo-butylric acid,
35 (146) 4-[3-(3,4-difluoro-benzyl)-phenyl]-2,4-dioxo-butylric acid,

- (147) 4-[3-(2,5-dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
(148) 4-[3-(2-chloro-6-methyl-benzyl)phenyl]-2,4-dioxobutyric acid,
(149) 2,4-dioxo-4-[3-(2-trifluoromethyl-4-chloro-benzyl)-phenyl]-
butyric acid,
5 (150) 4-[3-(2-bromo-5-chloro-benzyl)-phenyl]-2,4-dioxo-butyric
acid,
(151) 4-(3-naphthalen-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
(152) 2,4-dioxo-4-[3-(3-fluorobenzyl)phenyl]butyric acid,
(153) 2,4-dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
10 (154) 2,4-dioxo-4-[3-(1-phenylethyl)phenyl]butyric acid,
(155) 4-(3-benzyl-4,5-dimethylphenyl)-2,4-dioxo-butyric acid,
(156) 2,4-dioxo-4-[3-(3-methoxybenzyl)phenyl]butyric acid,
(157) 4-[3-(5-methyl-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyric
acid,
15 (158) 4-[3-(5-chloro-thiophen-2-ylmethyl)phenyl]-2,4-dioxo-butyric
acid,
(159) 4-(3-benzyl-5-methylphenyl)-2,4-dioxo-butyric acid,
(160) 4-[3-(2-cyanobenzyl)phenyl]-2,4-dioxo-butyric acid,
(161) 4-[3-benzylphenyl]-2,4-dioxobutyric acid,
20 (162) 4-[3-(3,5-dichloro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
(163) 4-(5-benzyl-2,4-dimethylphenyl)-2,4-dioxo-butyric acid,
(164) 4-(5-benzyl-2-methylphenyl)-2,4-dioxo-butyric acid,
(165) 4-(3-cyclohexylmethyl-phenyl)-2,4-dioxo-butyric acid,
(166) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-
butyric acid,
25 (167) 4-[3-benzyl-5-(5-hydroxy-pentyl)-phenyl]-2,4-dioxo-butyric
acid,
(168) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
(169) 4-[3-(3-tert-butoxy-2-hydroxy-propyl)-5-(2-methyl-benzyl)-
phenyl]-2,4-dioxo-butyric acid,
30 (170) 2,4-dioxo-4-[3-(2,3-dimethoxy-benzyl)-phenyl]-butyric acid,
(171) 4-[3-(methoxyphenylmethyl)phenyl]-2,4-dioxobutyric acid,
(172) 4-[3-[hydroxy-(tetrahydro-furan-3-yl)-methyl]-5-(2-methyl-
benzyl)-phenyl]-2,4-dioxo-butyric acid,
35 (173) 2,4-dioxo-4-(3-phenoxy-methyl-phenyl)-butyric acid,

- (174) 2,4-dioxo-4-(3-phenoxy-methyl-phenyl)-butyric acid,
(175) 4-[3-benzyl-5-(cyclopropylcarboxamido)-phenyl]-2,4-dioxobutyric acid,
(176) 4-[3-benzyl-5-(t-butoxycarbamoyl)phenyl]-2,4-dioxobutyric acid,
5 (177) 4-[3-(hydroxy-phenyl-methyl)-phenyl]-2,4-dioxo-butyric acid,
(178) 4-[5-benzyl-2,3-dimethylphenyl]-2,4-dioxo-butyric acid,
(179) n-[3-(3,5-dibromobenzyl)phenyl]-2,4-dioxo-butyric acid,
(180) 4-[3-(2-methyl-benzyl)-5-pyrimidin-2-yl-phenyl]-2,4-dioxo-butyric acid,
10 (181) 4-[3-benzyl-2-(pyrimidin-2-ylamino)-phenyl]-2,4-dioxo-butyric acid
(182) 4-[3-benzoimidazol-1-ylmethyl-5-(2-methyl-benzyl)-phenyl]-2,4-dioxo-butyric acid,
15 (183) 2,4-dioxo-4-[3-(3-trifluoromethylbenzyl)phenyl] butyric acid,
(184) 4-(4-phenoxy-phenyl)-2,4-dioxo-butyric acid,
(185) 2,4-dioxo-4-(3-[1,2,3]triazol-2-ylmethyl-phenyl)-butyric acid,
(186) 4-[3-benzyl-5-(6-methoxy-pyridin-2-yl)-phenyl]-2,4-dioxo-butyric acid,
20 (187) 4-(3-benzotriazol-2-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
(188) 4-[3-benzyl-5-(2-(4-methylpiperazin-1-yl)-pyrazin-6-yl)phenyl]-2,4-dioxobutyric acid,
(189) 4-[4-(3-phenethyl)phenyl]-2,4-dioxobutyric acid,
(190) 4-[4-(3-chlorobenzyl)phenyl]-2,4-dioxobutyric acid,
25 (191) 4-(3-benzoimidazol-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
(192) 4-[3-benzyloxy-5-(6-tert-butoxycarbonylamino-hexyloxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid,
(193) 4-(3-benzotriazol-1-ylmethyl-phenyl)-2,4-dioxo-butyric acid,
30 (194) 4-[3-(3,5-dimethyl-pyrazol-1-ylmethyl)-phenyl]-2,4-dioxo-butyric acid,
(195) 4-[3-benzyloxy-5-(2-morpholin-4-yl-ethoxy)phenyl]-2-hydroxy-4-oxo-but-2-enoic acid,
(196) 4-(4-methyl-3-phenoxy-phenyl)-2,4-dioxo-butyric acid
35 (197) 4-[3-(2-hydroxy-benzyl)-phenyl]-2,4-dioxo-butyric acid,

- (198) 4-[3-benzyl-5-(6-dimethylamino-pyrazin-2-yl)-phenyl]-2,4-dioxo-butyric acid, and
(199) 4-(5-benzyl-2-methoxypyridin-3-yl)-2,4-dioxobutyric acid;
and tautomers and pharmaceutically acceptable salts thereof.

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15. The compound according to Claim 14 selected from:

- (1) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,
(2) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-
butyric acid,
10 (3) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-
butyric acid,
(4) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
(5) 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-
phenyl]butyric acid,
15 (6) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
(7) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
(8) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-
butyric acid,
(9) 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyric acid,
20 (10) 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-
dioxobutyric acid,
(11) 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid,
(12) 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric
acid,
25 (13) 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
(14) 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-
dioxobutyric acid,
(15) 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-
butyric acid,
30 (16) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric
acid,
(17) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-
dioxobutyric acid,
(18) 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric
35 acid,

- (19) 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (20) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid,
- 5 (21) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (22) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (23) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-dioxobutyric acid,
- 10 (24) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (25) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (26) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-butyric acid,
- 15 (27) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyric acid,
- (28) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (29) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyric acid, and
- 20 (30) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-dioxo-butyric acid;
- and tautomers and pharmaceutically acceptable salts thereof.

25 16. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and an effective amount of a compound according to Claim 1.

30 17. The pharmaceutical composition of Claim 16, useful for treating infection by HIV, or for treating AIDS or ARC.

18. The pharmaceutical composition according to Claim 17 additionally comprising a therapeutically effective amount of an AIDS treatment agent selected from

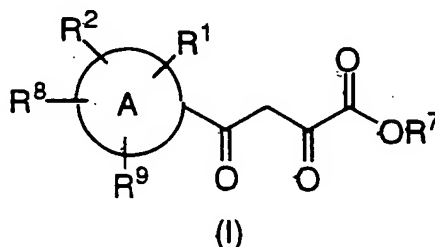
35 (1) an AIDS antiviral agent,

- (2) an anti-infective agent, and
- (3) an immunomodulator.

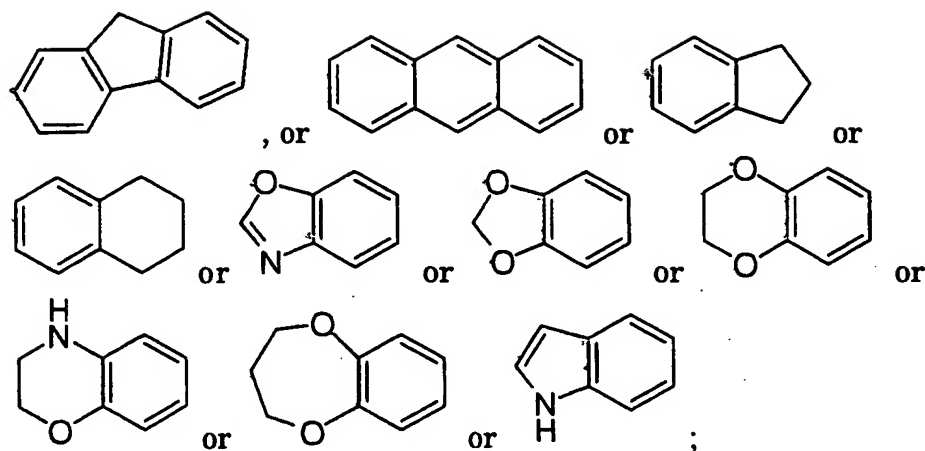
19. The composition of Claim 18 wherein the antiviral
5 agent is an HIV protease inhibitor.

20. The composition of Claim 19 wherein the HIV
protease inhibitor is N-(2(R)-hydroxy-1-(S)-indanyl)-2(R)-phenylmethyl-
4(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-
10 piperazinyl))-pentaneamide or a pharmaceutically acceptable salt
thereof.

21. A method of inhibiting HIV integrase, comprising
the administration to a mammal in need of such treatment a
15 therapeutically effective amount of a compound of structural formula
(I):



and tautomers and pharmaceutically acceptable salts thereof,
20 wherein:
A is a six-membered aromatic or heteroaromatic ring containing 0, 1, or
2 nitrogen heteroatoms substituted on carbon or nitrogen by R¹, R², R⁸,
and R⁹;
optionally the aromatic ring may be fused with another ring system to
25 form:



R¹ is selected from:

- 5 (1) -H,
- (2) -C₁₋₅ alkyl,
- (3) -C₁₋₆ alkyl-OR⁷,
- (4) -O-C₁₋₆ alkyl-OR⁷,
- (5) -O-C₁₋₆ alkyl-SR⁷,
- 10 (6) -CF₃ or -CH₂CF₃,
- (7) -halo,
- (8) -NO₂,
- (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
- (10) -R⁶,
- 15 (11) -C₂₋₅ alkenyl-R³,
- (12) -C₂₋₅ alkynyl-R³,
- (13) -O-R⁶,
- (14) -O-C₁₋₆ alkyl, wherein one or more of the hydrogen atoms
 may be replaced with fluorine atoms,
- 20 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷;
- (16) -O-C₂₋₆ alkyl-N(R⁴)(R⁵);
- (17) -S-C₁₋₃ alkyl;
- (18) -C(O)CH₂C(O)C(O)OR⁷;
- (19) -CH₂-CH(OH)-CH₂-O-R⁷; and
- 25 (20) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);

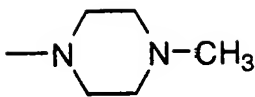
R² is selected from:

- (1) -H,
- (2) -R³,

- (3) -C₁₋₆ alkyl,
- (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the hydrogen atoms on C₁₋₆ alkyl may be replaced with a fluorine atom,
- 5 (5) -C₂₋₆ alkenyl,
- (6) -O-R⁶,
- (7) -O-C₁₋₆ alkyl-OR⁶,
- (8) -O-C₁₋₆ alkyl-SR⁶,
- (9) -S(O)_n-R⁶,
- 10 (10) -C₁₋₆ alkyl (OR⁶)(R⁴),
- (11) -C₀₋₆ alkyl-N(R⁴)(R⁶),
- (12) -C₁₋₆ alkyl S(O)_n-R⁶,
- (13) -C₀₋₆ alkyl C(O)-R⁶,
- (14) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
- 15 (15) -C₁₋₆ alkyl C(S)-R⁶,
- (16) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
- (17) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
- (18) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- 20 (1) a 5 or 6 membered aromatic or heteroaromatic ring, containing 0, 1, 2, 3, or 4 heteroatoms selected from oxygen, nitrogen and sulfur, unsubstituted or substituted on nitrogen or carbon by 1 to 5 substituents selected from:
 - (a) halogen,
 - 25 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen atoms may be replaced with a fluorine atom,
 - (d) phenyl,
 - 30 (e) -S-C₁₋₆ alkyl,
 - (f) -CN,
 - (g) hydroxy,
 - (h) phenyloxy,
 - (i) -C₀₋₆ alkyl-N(R⁷)₂,



- (j)
- (k) oxo, and
- (l) substituted phenyloxy with 1, 2, or 3 substituents selected from:
- 5 (i) halogen,
(ii) C₁₋₆ alkyl,
(iii) -CF₃, and
(iv) hydroxy;
- (2) a 3 to 6 membered saturated ring containing 0, 1 or 2
10 heteroatoms selected from oxygen, nitrogen or sulfur,
unsubstituted or substituted with 1 to 5 substituents selected
from:
- (a) halogen,
(b) C₁₋₆ alkyl,
15 (c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O,
20 (h) benzyl, and
(i) hydroxy;
- (3) unsubstituted or substituted hexahydrothieno[3,4-
d]imidazolyl with one or two substituents selected from:
- (a) oxo,
25 (b) halogen,
(c) C₁₋₆ alkyl,
(d) C₁₋₆ alkyloxy-,
(e) -CF₃,
(f) -OCF₃,
30 (g) -CN, and
(h) hydroxy;
- (4) a 5 or 6 membered aromatic or heteroaromatic ring,
containing 0, 1, 2 or 3 heteroatoms selected from oxygen,

nitrogen and sulfur, fused with a phenyl ring; wherein the ring system is unsubstituted or substituted on a nitrogen or carbon atom by 1 to 3 substituents selected from:

- 5 (a) -halogen,
(b) -C₁₋₆ alkyl,
(c) -C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN, and
10 (g) -hydroxy;
- (5) a 3 to 6 membered saturated ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, fused with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:
- 15 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
20 (f) -CN,
(g) =O, and
(h) hydroxy;
- (6) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, containing 2 or 3 double bonds, unsubstituted or substituted with 1 or 2 substituents selected from:
- 25 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
30 (d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O, and
(h) hydroxy; and

- (7) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, containing 2 or 3 double bonds, fused with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:

- 5 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
10 (f) -CN,
(g) =O, and
(h) hydroxy; and

each R⁴ is independently selected from:

- (1) -H,
15 (2) -C₁₋₄ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₂₋₃ alkenyl,
(6) -C₁₋₃ alkyl-R³,
20 (7) -C₂₋₃ alkenyl-R³,
(8) -S(O)_n-R³, and
(9) -C(O)-R³;

each R⁵ is independently selected from:

- (1) -H,
25 (2) -C₁₋₃ alkyl,
(3) -CF₃,
(4) -R³,
(5) -C₂₋₃ alkenyl,
(6) -C₁₋₃ alkyl-R³,
30 (7) -C₂₋₃ alkenyl-R³,
(8) -S(O)_n-R³,
(9) -C(O)-R³,
(10) -C(O)OR⁴, and
(11) -C(O)C(O)OH;

35 each R⁶ is independently selected from:

(1) -C₁₋₃ alkyl-R³, and

(2) -R³;

each R⁷ is independently selected from:

(1) -H, and

5 (2) -C₁₋₆ alkyl;

R⁸ is selected from:

(1) -H,

(2) -O- C₁₋₆ alkyl and

(3) C₁₋₆ alkyl;

10 R⁹ is selected from:

(1) -H,

(2) -O- C₁₋₃ alkyl,

(3) -OH, and

(4) oxo; and

15 each n is independently selected from 0, 1 and 2.

22. The method according to Claim 21, wherein the compound of structural formula (I) is selected from:

(1) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,

20 (2) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-butyrlic acid,

(3) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-butyrlic acid,

(4) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyrlic acid,

25 (5) 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-phenyl]butyrlic acid,

(6) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyrlic acid,

(7) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyrlic acid,

(8) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-

30 butyrlic acid,

(9) 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyrlic acid,

(10) 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-

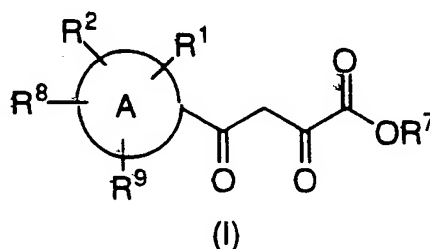
dioxobutyrlic acid,

(11) 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyrlic acid,

- (12) 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric acid,
- (13) 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
- (14) 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-dioxobutyric acid,
- (15) 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-butyric acid,
- (16) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric acid,
- (17) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-dioxobutyric acid,
- (18) 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric acid,
- (19) 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (20) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid,
- (21) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (22) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (23) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-dioxobutyric acid,
- (24) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (25) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (26) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-butyric acid,
- (27) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyric acid,
- (28) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (29) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyric acid, and

- (30) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-dioxo-butyrlic acid; and tautomers and pharmaceutically acceptable salts thereof.

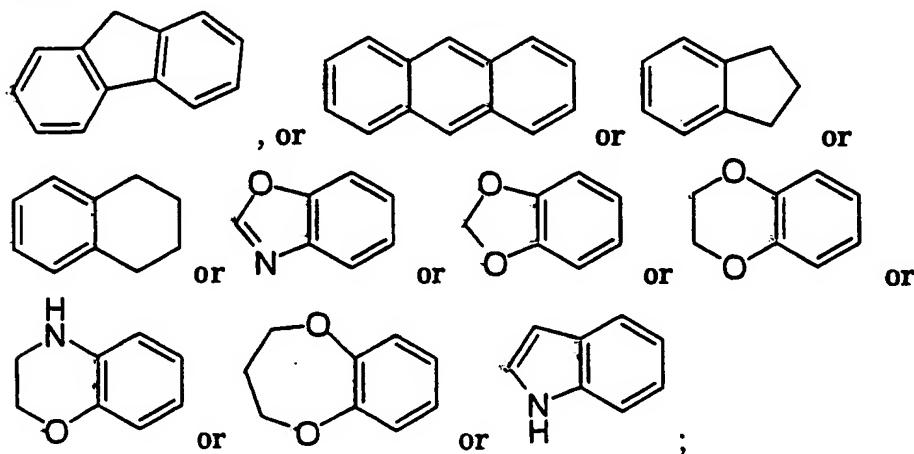
- 5 23. A method of treating infection by HIV, or of treating AIDS or ARC, comprising the administration to a human in need of such treatment a therapeutically effective amount of a compound of structural formula (I):



- 10 and tautomers and pharmaceutically acceptable salts thereof, wherein:

A is a six-membered aromatic or heteroaromatic ring containing 0, 1, or 2 nitrogen heteroatoms substituted on carbon or nitrogen by R¹, R², R⁸, and R⁹;

- 15 optionally the aromatic ring may be fused with another ring system to form:



- 20 R¹ is selected from:

- (1) -H,
- (2) -C₁₋₅ alkyl,

- (3) -C₁₋₆ alkyl-OR⁷,
 (4) -O-C₁₋₆ alkyl-OR⁷,
 (5) -O-C₁₋₆ alkyl-SR⁷,
 (6) -CF₃ or -CH₂CF₃,
 5 (7) -halo,
 (8) -NO₂,
 (9) -C₀₋₃ alkyl -N(R⁴)(R⁵),
 (10) -R⁶,
 (11) -C₂₋₅ alkenyl-R³,
 10 (12) -C₂₋₅ alkynyl-R³,
 (13) -O-R⁶,
 (14) -O-C₁₋₆ alkyl, wherein one or more of the hydrogen atoms
 may be replaced with fluorine atoms,
 (15) -O-C₁₋₆ alkyl-NH-C(O)-OR⁷,
 15 (16) -O-C₂₋₆ alkyl-N(R⁴)(R⁵),
 (17) -S-C₁₋₃ alkyl,
 (18) -C(O)CH₂C(O)C(O)OR⁷,
 (19) -CH₂-CH(OH)-CH₂-O-R⁷, and
 (20) -C(OH)(CH₃)-CH₂N(R⁴)(R⁵);
- 20 R² is selected from:
- (1) -H,
 (2) -R³,
 (3) -C₁₋₆ alkyl,
 (4) -C₁₋₆ alkyl substituted with R³, wherein one or more of the
 25 hydrogen atoms on C₁₋₆ alkyl may be replaced with a
 fluorine atom,
 (5) -C₂₋₆ alkenyl,
 (6) -O-R⁶,
 (7) -O-C₁₋₆ alkyl-OR⁶,
 30 (8) -O-C₁₋₆ alkyl-SR⁶,
 (9) -S(O)_n-R⁶,
 (10) -C₁₋₆ alkyl (OR⁶)(R⁴),
 (11) -C₀₋₆ alkyl-N(R⁴)(R⁶),
 (12) -C₁₋₆ alkyl S(O)_n-R⁶,

- (13) -C₀₋₆ alkyl C(O)-R⁶,
 (14) -C₀₋₆ alkyl C(O)CH₂-C(O)-OH,
 (15) -C₁₋₆ alkyl C(S)-R⁶,
 (16) -C₁₋₆ alkyl NR⁴C(O)-R⁶,
 5 (17) -C₁₋₆ alkyl-C(O)N(R⁴)(R⁵), and
 (18) -CH₂(OR⁷)-R⁶;

each R³ is independently selected from:

- (1) a 5 or 6 membered aromatic or heteroaromatic ring,
 containing 0, 1, 2, 3, or 4 heteroatoms selected from oxygen,
 10 nitrogen and sulfur, unsubstituted or substituted on
 nitrogen or carbon by 1 to 5 substituents selected from:
 (a) halogen,
 (b) C₁₋₆ alkyl, wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 15 (c) C₁₋₆ alkyloxy- wherein one or more of the hydrogen
 atoms may be replaced with a fluorine atom,
 (d) phenyl,
 (e) -S-C₁₋₆ alkyl,
 (f) -CN,
 20 (g) hydroxy,
 (h) phenoxy,
 (i) -C₀₋₆ alkyl-N(R⁷)₂,

$$\text{---N} \begin{array}{c} \diagup \quad \diagdown \\ | \quad | \\ \diagdown \quad \diagup \end{array} \text{N-CH}_3$$

 (j) ,
 (k) oxo, and
 25 (l) substituted phenoxy with 1, 2, or 3 substituents
 selected from:
 (i) halogen,
 (ii) C₁₋₆ alkyl,
 (iii) -CF₃, and
 30 (iv) hydroxy;
- (2) a 3 to 6 membered saturated ring containing 0, 1 or 2
 heteroatoms selected from oxygen, nitrogen or sulfur,

- unsubstituted or substituted with 1 to 5 substituents selected from:
- (a) halogen,
 - (b) C₁₋₆ alkyl,
 - 5 (c) C₁₋₆ alkyloxy-,
 - (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN,
 - (g) =O,
 - 10 (h) benzyl, and
 - (i) hydroxy;
- (3) unsubstituted or substituted hexahydrothieno[3,4-d]imidazolyl with one or two substituents selected from:
- (a) oxo,
 - 15 (b) halogen,
 - (c) C₁₋₆ alkyl,
 - (d) C₁₋₆ alkyloxy-,
 - (e) -CF₃,
 - (f) -OCF₃,
 - 20 (g) -CN, and
 - (h) hydroxy;
- (4) a 5 or 6 membered aromatic or heteroaromatic ring, containing 0, 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulfur, fused with a phenyl ring; wherein the
- 25 ring system is unsubstituted or substituted on a nitrogen or carbon atom by 1 to 3 substituents selected from:
- (a) -halogen,
 - (b) -C₁₋₆ alkyl,
 - (c) -C₁₋₆ alkyloxy-,
 - 30 (d) -CF₃,
 - (e) -OCF₃,
 - (f) -CN, and
 - (g) -hydroxy;
- (5) a 3 to 6 membered saturated ring containing 0, 1 or 2
- 35 heteroatoms selected from oxygen, nitrogen or sulfur, fused

with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:

- 5 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O, and
10 (h) hydroxy;
- (6) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, containing 2 or 3 double bonds, unsubstituted or substituted with 1 or 2 substituents selected from:
- 15 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
(d) -CF₃,
(e) -OCF₃,
20 (f) -CN,
(g) =O, and
(h) hydroxy; and
- (7) a 5 to 6 membered ring containing 0, 1 or 2 heteroatoms selected from oxygen, nitrogen or sulfur, containing 2 or 3 double bonds, fused with a phenyl ring, unsubstituted or substituted with 1 or 2 substituents selected from:
- 25 (a) halogen,
(b) C₁₋₆ alkyl,
(c) C₁₋₆ alkyloxy-,
30 (d) -CF₃,
(e) -OCF₃,
(f) -CN,
(g) =O, and
(h) hydroxy; and
- 35 each R⁴ is independently selected from:

- (1) -H,
- (2) -C₁₋₄ alkyl,
- (3) -CF₃,
- (4) -R³,
- 5 (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₃ alkyl-R³,
- (7) -C₂₋₃ alkenyl-R³,
- (8) -S(O)_n-R³, and
- (9) -C(O)-R³;

10 each R⁵ is independently selected from:

- (1) -H,
- (2) -C₁₋₃ alkyl,
- (3) -CF₃,
- (4) -R³,
- 15 (5) -C₂₋₃ alkenyl,
- (6) -C₁₋₃ alkyl-R³,
- (7) -C₂₋₃ alkenyl-R³,
- (8) -S(O)_n-R³,
- (9) -C(O)-R³,
- 20 (10) -C(O)OR₄, and
- (11) -C(O)C(O)OH;

each R⁶ is independently selected from:

- (1) -C₁₋₃ alkyl-R³, and
- (2) -R³;

25 each R⁷ is independently selected from:

- (1) -H, and
- (2) -C₁₋₆ alkyl;

R⁸ is selected from:

- (1) -H,
- 30 (2) -O- C₁₋₆ alkyl and
- (3) C₁₋₆ alkyl;

R⁹ is selected from:

- (1) -H,
- (2) -O- C₁₋₃ alkyl,
- 35 (3) -OH, and

(4) oxo; and
each n is independently selected from 0, 1 and 2.

24. The method according to Claim 23 wherein the
5 compound of structural formula (I) is selected from:

- (1) 4-(3-Benzylphenyl)-2,4-dioxobutanoic acid,
- (2) 4-[3-(5-methyl-thiophen-2-ylmethyl)-phenyl]-2,4-dioxo-
butyric acid,
- (3) 4-[3-[(methyl-phenyl-amino)-methyl]-phenyl]-2,4-dioxo-
10 butyric acid,
- (4) 4-(3-benzyl-5-pyrazin-2-yl-phenyl)-2,4-dioxo-butyric acid,
- (5) 2,4-dioxo-4-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-
phenyl]butyric acid,
- (6) 2,4-Dioxo-4-(3-phenylsulfanyl-phenyl)-butyric acid,
- (7) 4-[3-(2,4-Difluoro-benzyl)-phenyl]-2,4-dioxo-butyric acid,
15 (8) 4-[5-(4-Fluoro-benzyl)-2,3-dimethoxy-phenyl]-2,4-dioxo-
butyric acid,
- (9) 4-(5-Benzyl-2-isopropoxyphenyl)-2,4-dioxobutyric acid,
- (10) 4-[5-Benzyl-2-(2-N,N-dimethylaminoethoxy)phenyl]-2,4-
dioxobutyric acid,
20 (11) 4-[5-Benzyl-2-(pyridin-2-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (12) 4-(5-Benzyl-2-isopropoxy-3-methoxyphenyl)-2,4-dioxo-butyric
acid,
- (13) 4-(5-Benzyl-2,3-dimethoxyphenyl)-2,4-dioxobutyric acid,
- (14) 4-(5-Benzyl-3-dimethylamino-2-methoxyphenyl)-2,4-
dioxobutyric acid,
25 (15) 4-[5-Benzyl-2-N,N-dimethylaminobenzoxazol-7-yl]-2,4-dioxo-
butyric acid,
- (16) 4-(3-Benzyl-5-pyrazin-2-ylmethylphenyl)-2,4-dioxobutyric
acid,
30 (17) 4-(3-Benzyl-5-[1,2,3]triazol-2-ylmethylphenyl)-2,4-
dioxobutyric acid,
- (18) 4-[3-(3-Chloropyridin-2-ylmethyl)phenyl]-2,4-dioxobutyric
acid,

- (19) 4-[5-Benzyl-2-methoxy-3-(N,N-dimethylaminomethyl)phenyl]-2,4-dioxo-butyric acid,
- (20) 4-(5-benzyl-3-methoxy-2-methoxyethoxyphenyl)-2,4-dioxobutyric acid,
- 5 (21) 4-(5-Benzyl-2-isopropoxy-3-[1,2,3]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (22) 4-(5-Benzyl-2-isopropoxy-3-[1,2,4]triazol-1-ylmethylphenyl)-2,4-dioxobutyric acid,
- (23) 4-[5-Benzyl-2-(3-N,N-dimethylaminopropoxy)-3-methoxyphenyl]-2,4-dioxobutyric acid,
- 10 (24) 4-[3-(Phenyldifluoromethyl)phenyl]-2,4-dioxobutyric acid,
- (25) 4-(5-Benzyl-2-cyclopropyloxyphenyl)-2,4-dioxobutyric acid,
- (26) 4-[5-Benzyl-2-isopropoxy-3-(1-piperidinylmethyl)phenyl]-2,4-dioxo-butyric acid,
- 15 (27) 4-[5-Benzyl-2-(2-dimethylamino-1-methylethoxy)phenyl]-2,4-dioxo-butyric acid,
- (28) 4-[5-Benzyl-2-(1-methylpiperidin-4-yloxy)phenyl]-2,4-dioxo-butyric acid,
- (29) 4-[3-Benzyl-5-(4-benzylpiperazin-1-yl)phenyl]-2,4-dioxo-butyric acid, and
- 20 (30) 4-[5-Benzyl-2-isopropoxy-3-(pyridin-2-ylaminomethyl)phenyl]-2,4-dioxo-butyric acid;
- and tautomers and pharmaceutically acceptable salts thereof.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US99/12093

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS online

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,336,397 A (CRAGOE, Jr. et al) 22 June 1982, especially col. 2, line 55 - col. 3 line 24.	1-9, 16
X	US 4,423,063 A (ROONEY et al) 27 December 1989, especially col. 2, line 55 - col. 3, line 22.	1-9, 16
X	EP 0 418 845 A1 (FUJISAWA PHARMACEUTICAL CO., LTD) 27 March 1991, especially page 25, line 14 and page 25, line 37.	1-9, 16
X	TANAKA, J. et al. Studies on Aromatic Sesquiterpenes. XI. Synthesis of 7-Isopropyl-3,5-dimethyl-1-naphthol. Bull. Chem. Soc. Jpn. 1989, Vol. 62, No. 6, pages 2102-2104, especially compound 9 page 2102.	1-9, 16

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

A	document defining the general state of the art which is not considered to be of particular relevance	*T*	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
E	earlier document published on or after the international filing date	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
L	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
O	document referring to an oral disclosure, use, exhibition or other means	*A*	document member of the same patent family
P	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

06 OCTOBER 1999

Date of mailing of the international search report

29 OCT 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
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PARALEGAL SPECIALIST
CHEMICAL MATRIX

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12093

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MURRAY et al. A Simple Regioselective Synthesis of Ethyl 1,5-Diarylpyrazole-3-carboxylates. J. Heterocyclic Chem. September-October 1989, Vol. 26, pages 1389-1392, especially compounds 1-7 in table 1 page 1389.	1-9, 16
X	FRERI, M. Deviazioni nella condensazione di Claisen. Gazz. Chim. Ital. 1938, Vol. 68, pages 612-618, see the whole paper especially compounds II, III, IV, V, and VI.	1-9, 16
X	US 3,899,508 A (WIKEL) 12 August 1975, especially below col. 2 see the intermediate - various alkyl esters and col. 3 lines 1-2.	1-2, 16
X	WITIAK, T et al. Synthesis of Ethyl 6-Substituted-Chroman- and -Chromone-2-carboxylates. A Comparative Structure-Activity Study Employing the 6-Phenyl and Phenoxy Analogs in the Triton Hyperlipidemic Rat Model. Journal of Medicinal Chemistry. 1975, Vol. 18, No. 9, pages 934-942, especially compounds 19, 20, and 40 on page 935.	1-9, 16
X	TOMASSINI, J. et al. Inhibition of Cap (m ⁷ GpppXm)-Dependent Endonuclease of Influenza Virus by 4-Substituted 2,4-Dioxobutanoic Acid Compounds. Antimicrobial Agents and Chemotherapy. December 1994, Vol. 38, No. 12, pages 2827-2837, especially compound 5 on page 2829.	1-9, 16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12093

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10-12
because they relate to subject matter not required to be searched by this Authority, namely:

The claims were searched to the point where the core substituent A was phenyl. The multitude of permutations that result because of the variable core meant that no meaningful search could be done on permutations other than phenyl. Thus, claims 10-12 were not searched.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/12093

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/535; A01N 37/08, 37/12, 43/02, 43/06, 43/26, 43/32, 43/38, 43/40, 43/54, 43/65, 43/58, 43/60, 43/64, 43/76, 43/82, 53/00; C07C 59/74, 59/76, 59/90, 69/76, 229/00, 321/00

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/239.2, 238.8, 247, 255, 256, 317, 360, 374, 381, 383, 406, 415, 438, 450, 452, 467, 530, 531, 538, 539, 541;
560/19, 48, 51, 53; 562/426, 433, 441, 451, 452, 457, 459, 462, 463

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/239.2, 238.8, 247, 255, 256, 317, 360, 374, 381, 383, 406, 415, 438, 450, 452, 467, 530, 531, 538, 539, 541;
560/19, 48, 51, 53; 562/426, 433, 441, 451, 452, 457, 459, 462, 463